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ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice

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SPECIAL ISSUE
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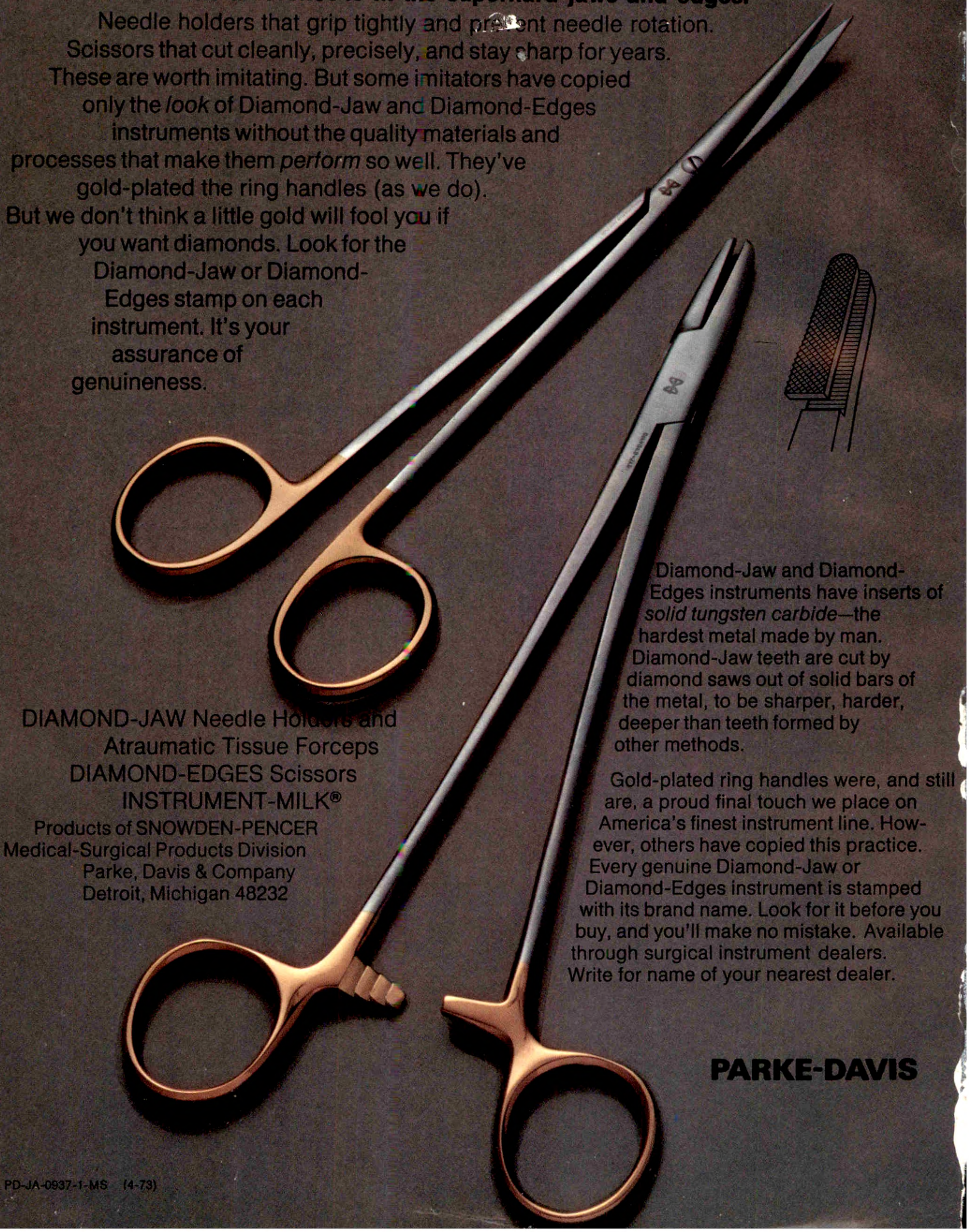

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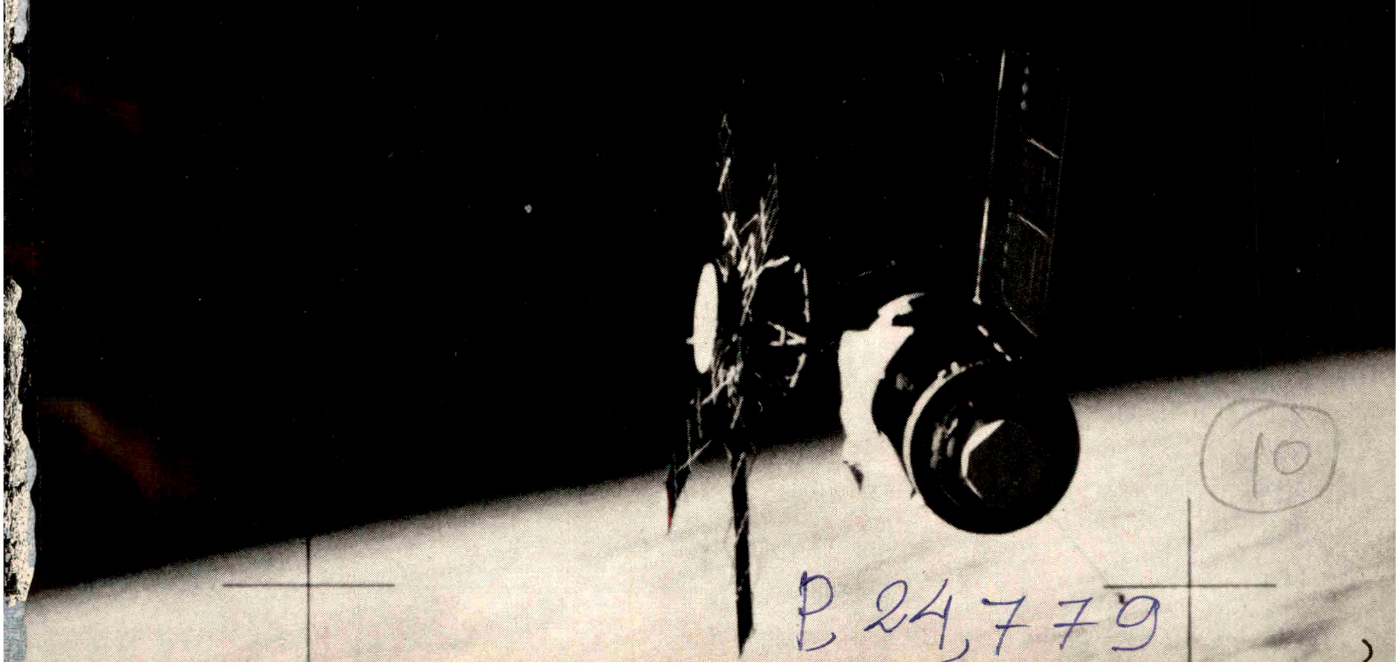

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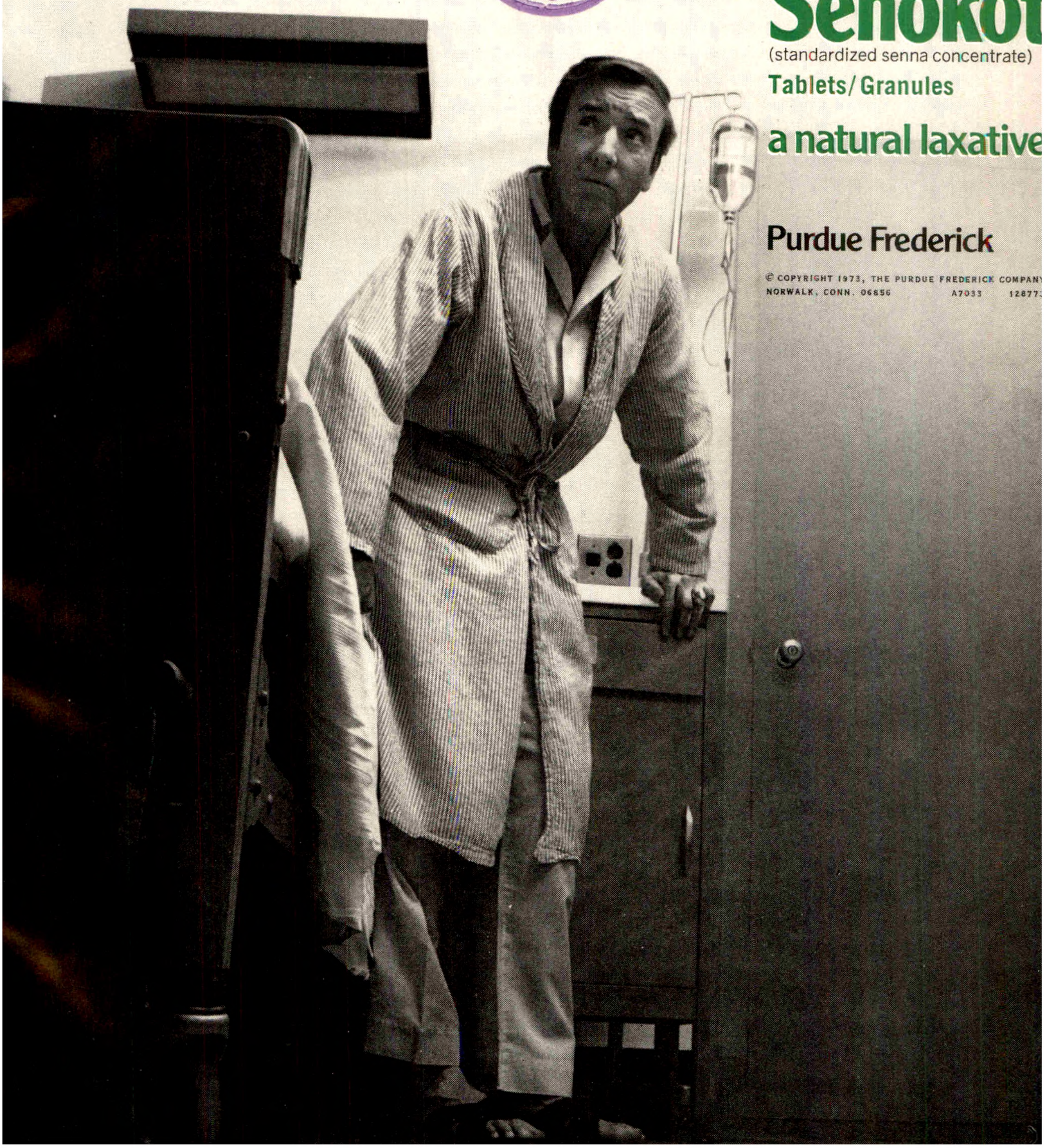

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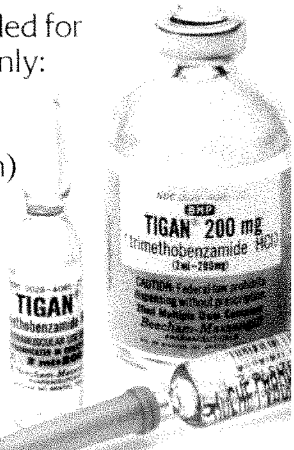

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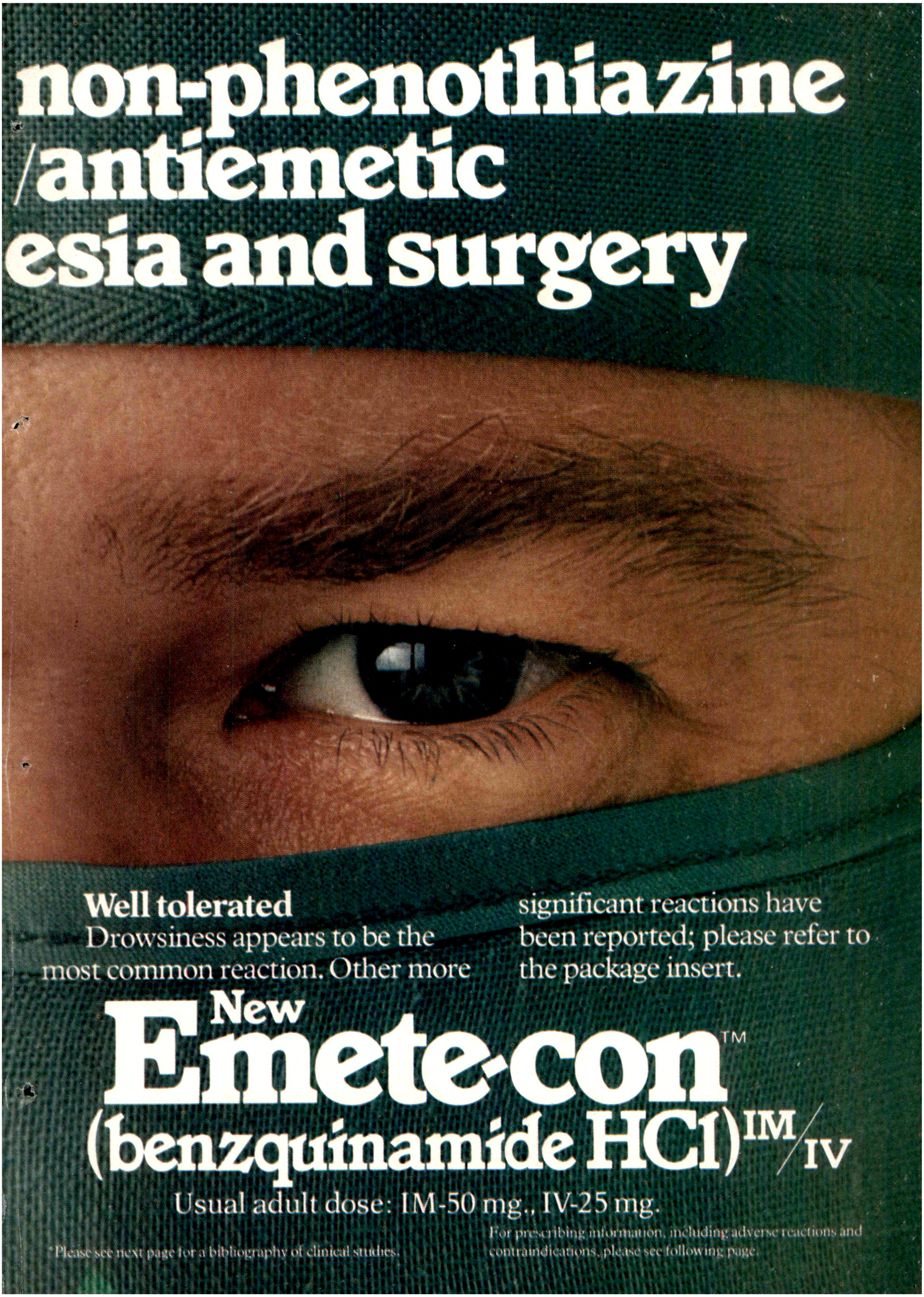

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Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. Because of the multiplicity of medications commonly used in the practice of anesthesia, unequivocal relationship to a specific drug administered usually cannot be established. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected—*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg–1.0 mg/kg)

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Intravenous: 25 mg (0.2 mg/kg–0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended.

This preparation must be initially reconstituted with 2.2 ml of sterile water. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature.
DO NOT REFRIGERATE.

Overdosage. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

Caution. Federal law prohibits dispensing without prescription.

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ANNALS OF SURGERY

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Presidential Address:

Professional Freedom and Governmental Control

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From the Department of Surgery,
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Nashville, Tennessee

I WOULD LIKE TO EXPRESS my deep gratitude to you, the fellows of the American Surgical Association, for the great honor you have done me in permitting me to serve as your President. I must affirm to you that my gratitude greatly exceeds my competence. Although it is probably presumptuous of me, I have chosen to address the conflicts which hang so uneasily over American surgeons today under the title "Professional Freedom and Governmental Control."

Freedom is the exciting ideal which has guided the destiny of individuals and of nations since the emergence of the Greeks from barbarism. Throughout recorded history freedom has had many meanings and many differing interpretations. To be free in ancient Greece and Rome implied exemption or release from slavery or imprisonment. The Greeks extolled the idea of personal liberty as the power of self-determination. In the Dark Ages and in medieval times the "free man" enjoyed freedom from bondage or indebtedness.

Martin Luther's break with the Catholic church in the early 16th century was a revolutionary manifestation of freedom of thought in ecclesiastical matters from one viewpoint and heresy from the other. The impact of Luther's free thinking both fractured and reshaped Western civilization. It is often said that the Pilgrims and the Puritans came to America to find freedom of religion. This freedom, however, for the most part concerned only their own particular religion. Puritans in Massachusetts Bay Colony were indeed free to worship God as they saw fit, but Quakers who tried to exercise the same right were sometimes abused, beaten and even hanged by the Puritans. Roger Williams broke with the Puritans in the 1630's over the question of freedom of religion and after his banishment from the Bay Colony, he raised the banner of democratic freedom in founding the settlement of Providence in Rhode Island, where religious freedom to Quakers, Jews, Catholics and Protestants was first granted by the colonists. In the early 18th century, Bishop Berkeley stated that "A man is said to be free so far forth as he can do what he will."

Americans have always been thrilled by Patrick Henry's stirring words, "Give me liberty or give me death," which fired our colonial ancestors to revolt against the British king and to fight for freedom from the "slavery and chains" of colonial subjugation to the crown of Britain. Orators in many lands have often cried, "give me liberty" or "give us liberty." Much less often has one said, "give *them* liberty." This nation's great historic exception came with Lincoln's Emancipation Proclamation and the war accompanying it which abolished slavery and established a basic freedom for all Americans.

For the right to think, worship and express opinion, men and women from earliest recorded history have been willing to lay down their lives. The democratic freedom which we enjoy in America today has evolved from the basic conflict between the ancient wish of the

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Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

individual to do as he pleases and the societal restrictions imposed on his behavior by ethics, morality and a system of laws.

At the time of framing the Constitution of the United States, Thomas Jefferson and his co-workers were keenly aware that the greatest threat to freedom of the individual was the tyranny of government. The Bill of Rights with its ten articles, adopted in 1791, amended the Constitution to stipulate the fundamental ways in which the civil liberties of the individual are protected from potential governmental tyranny.

The first amendment to the Constitution, Article I of the Bill of Rights, decrees: "Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble, and to petition the government for a redress of grievances."

We, the fellows of the American Surgical Association, are peaceably assembled for our 94th annual meeting to enjoy the excellent scientific papers which our program committee has selected and the vigorous discussions which they will surely evoke in an exemplary demonstration of freedom of speech (although not to exceed ten minutes for essayists and three minutes for discussants). In this beautiful Colorado setting we have already begun to enjoy the good fellowship for which this Association is noted and the superb arrangements of the local committee.

We are on the whole a group of reasonably well educated, surely well qualified, and certainly well nourished surgical specialists who are products of a free society and a free enterprise system. We and our peers in medicine in the United States have enjoyed in our lifetimes an extraordinary degree of professional freedom. Possibly more than our descendants will ever be able to imagine. Our pluralistic system of medical and surgical care has evolved as part of the free enterprise basis of our national economy. The fellows of the American Surgical Association have contributed richly in the last 90 years to the advances in medical education and knowledge, in surgical training and treatment, and to the high standards of surgical practice and quality care which have established American surgery in a position of leadership throughout the world in the view of most of our professional peers abroad and at least one American lay writer and political analyst, Mr. Harry Schwartz.

However, it has been brought home to us in the last several years by the politicians, the news media, the journalists and by the addresses of the recent presidents of this association, beginning with William Altemeier and continuing with William Holden, Francis Moore and Jonathan Rhoads, that American surgeons have a tarnished image and that our professional freedoms, as well as our pluralistic system of medical and surgical care, are in jeopardy as never before in the history of our nation. The principal source of the attack on our professional freedom is not located in Peking, Hanoi or Moscow. Rather, the headquarters is in Washington, D.C.

In 1847 Ralph Waldo Emerson made the following observation: "The name of Washington City in the newspapers is every day of blacker shade. All the news from that quarter being of a sadder type, more malignant. It seems to be settled that no act of honor or benevolence or justice is to be expected from the American government, but only this, that they will be as wicked as they dare. No man can have any sort of success in politics without a streak of infamy crossing his name."

In Emerson's use of the word "streak" he could not possibly have imagined its ridiculous present day connotation. If Emerson were to come alive today and could view the Washington scene, he would hardly be surprised by the Watergate scandals, the multiple indictments of high governmental officials including the former Vice President, the serious consideration in the Congress of impeachment of the President of the United States, nor by the sadistic and malignant treatment of these topics by the news media. However, I am persuaded that Emerson, as a protagonist of personal and professional freedom, would be shocked and horrified to read through the list of bills recently enacted as law and those currently proposed by senators and congressmen in the area of health care and its delivery which further imperil the professional freedom of physicians and surgeons and which would replace our entire medical care system by tax supported collectivistic, socialistic plans of national health care for "providers", "vendors", and "consumers" under the multifacetted control of bureaus of the federal government.

Prior to World War II, the United States government followed a *laissez faire* policy in regard to our American pluralistic system of medical care. The U.S. Public Health Service had a well developed national program which related to all the states in the important areas of preventive medicine, sanitation, communicable disease control, biologic standards and vital statistics. The armed services maintained their own medical corps to attend military personnel. Their disabled veterans were cared for in a small number of Veterans Hospitals which were essentially old soldiers' homes.

In the period since World War II there has been a steadily increasing incursion of the federal government into all aspects of health and medical care. The huge Veterans Administration Hospital system with its medical care program has grown to enormous size since its reorganization in 1946. Under the early influence of its chief medical director, General Paul Hawley, later to become Director of the American College of Surgeons, a policy of association of the many new Veterans Hospitals with medical schools was developed and a part of the responsibility for elevating the standards of medical care for veterans was placed on medical school faculties. Despite the myriads of bureaucratic inefficiencies and problems in the conduct of the affairs of the Veterans Administration Hospital program and the criticism that it has been the single most expensive program for delivery of medical care the world has ever known, the Veterans Hospitals and their professional staff have provided good in-patient medical and surgical rehabilitative services to over 16 million of our population during the period 1946 through 1973. In addition, a majority of the 170 V.A. Hospitals have become firmly affiliated with medical schools and as teaching hospitals have provided strong support to the university programs of education and research. Currently, the V.A. employs about 6,000 full time physicians and at least one-third of these hold faculty appointments in medical schools. In addition, more than 10,000 physicians participate on a part-time or consultant basis and approximately 100,000 physicians are involved in a fee basis program outside of the V.A. facility. Approximately 10,000 residents rotate through the V.A. training programs each year and about 12,000 medical students are assigned annually to V.A. Hospital wards and laboratories. The V.A. has become the nation's largest health care system.

In 1953, President Eisenhower signed into law the bill which incorporated the U.S. Public Health Service into the Department of Health, Education and Welfare. The creation of such a department by our federal government was considered by many of its critics to embody the concept that the government was responding to socialistic political pressures to provide shelter for its citizens from the cradle to the grave.

Despite this valid criticism, in the next 18 years the promotion of research and the financing of research facilities, investigators, research trainees and technicians by the U.S. Public Health Service and other programs of H.E.W. achieved a level never before dreamed of by our scientific community. The guiding policies which were employed were wonderfully fair. These policies opposed directed research, promoted individual ingenuity and freedom of choice in problems for investigation and methodology to be used and developed a healthy competitive system for applicants under an excellent program of peer review. Awards and contracts were made on the basis of merit.

The Hill-Burton Hospital construction program brought federal subsidies to assist hundreds of communities in building well equipped modern hospitals during the decades of the 50's and 60's. By 1971 the program had provided federal funds for the construction of some 336,000 beds. In some communities these hospitals improved the quality of medical care by providing good facilities for the well qualified local physicians and surgeons and by attracting others with good qualifications. In many communities, however, the effect was the opposite. The availability of excellent facilities encouraged local staff members without the qualifications of training and experience to undertake management of problems, especially surgical problems, far beyond their capabilities.

In retrospect this relatively healthy symbiosis between the voluntary medical sector and the governmental medical programs of the 1950's and 60's brought many advantages for patients and physicians alike and enhanced the strength of American medicine. The booming economy and the enormous growth of private medical insurance forestalled the omnipresent socialistic pressures for governmental take-over of all medical care as had happened in 1948 in Great Britain.

However, in 1965 after years of political struggle in the Congress, President Johnson signed the Medicare-Medicaid legislation into law. Despite the humanitarian motives of the social planners and the liberal politicians who wished to provide tax-supported, so-called "free" medical care for the aged and for the poor, the federal regulations involved in implementation of the legislation and its modifying amendments have been decidedly mixed blessings and have deluged physicians and hospitals with bureaucratic red tape. The "cost-only" policies of payment to hospitals have actually had the effect of increasing the overall cost of medical care. The outright discrimination against teaching hospitals, residents in training and the practicing clinicians in teaching hospitals has shaken the financial stability of many of our leading institutions. These factors have had the effects of moving both Medicare patients and teaching physicians away from university centers.

Until the mid 1960's the proponents of governmental involvement in health and medical care were pretty much limited to social planners and liberal politicians. However, the enormous inflationary impetus which followed the enactment of Medicare and Medicaid gave them new allies. The concomitant massive governmental spending of both the Johnson and Nixon administrations supporting the Viet Nam war, building huge deficits and promoting rampant inflation, was apparently not as impressive to economy-minded Congressmen as were the rapidly rising costs of Medicare and Medicaid. A rather modest financial investment of the mid 60's suddenly became a major drain on tax resources and a significant contributor to the health cost inflationary cycle in which we currently find ourselves.

In 1950 the U.S.A. spent 10.4 billion dollars for health care and 3.3 billion dollars or twenty per cent came from the public treasury. By 1973 the total health care bill was 94.1 billion dollars and 31 billion or thirty-seven per cent derived from public funds. For fiscal year 1975 the budget proposed for health spending by Mr. Nixon is 35.5 billion dollars of which 20.7 billion is requested for Medicare and Medicaid.

With these enormous governmental expenditures for medical care, coupled with the recurring din of the lay press concerning "doctor shortages," "our archaic system of medical care," "the health care crisis," and other familiar clichés which impugn the value of American medicine, there have inevitably come the governmental cuts in sponsored programs, controls, reprisals, and the bills to establish various forms of national health insurance and tax-supported "free" medical care for everyone.

Let us briefly look at what has recently happened and what is apparently about to happen in these areas.

Under the guise of economy in federal spending the hatchet men of the Nixon administration have harshly terminated the productive period of symbiosis between the private medical sector and the federal government. Their abrasive changes in federal policy have included drastic cuts and impoundments of funds appropriated by Congress for research and research facilities; the ruthless phasing out of training grants, fellowships and many other programs for scientific manpower production; elimination of Hill-Burton Hospital construction, the Regional Medical programs, public and allied health personnel education, general research support grants for medical schools, capitation grants for schools of nursing and many other previously sponsored health programs. Further, the President's Office of Management and Budget has proposed as an "economy" the elimination of the excellent peer review system at the National Institutes of Health and as an alternative suggested that the review and award of contracts and grants be solely by NIH scientists and staff. The recent trend toward targeted and contract research at NIH must reflect these bureaucratic pressures.

In 1971, trapped by inflation and recession, President Nixon suddenly proclaimed an economic freeze followed by the first wage and price controls ever imposed on our nation in peace time. The Economic Stabilization Act of 1970 had established the Cost of Living Council and the power for the President to establish controls on the economy. The highly discriminatory controls on physicians' fees and the equally abusive controls on hospital charges and other phases of the health industry are now a matter of this administration's record.

In 1972 Public Law 09-603, popularly known as the Bennett Amendment to the Social Security Act, established the Professional Standards Review Organization (PSRO). The major provisions of this legislative authority include: 1) establishment of PSRO's which are to assure that health services paid for under Medicare, Medicaid and maternal and child health programs are medically necessary, meet professionally recognized standards, are appropriately provided in the most economical sites and to review hospital and other institutional care; 2) establishment of statewide PSR Councils to advise PSRO's; and 3) establishment of a National PSR Council to advise the Secretary of HEW and to review and assess PSRO's and state councils. PSRO's will be run by M.D.'s and will affect about 44 million Medicare and Medicaid recipients and about $22 billion in federal and state expenditures for Medicare and Medicaid and virtually all aspects of our health care system. While the underlying theory of PSRO is to improve the quality of medical care, the fundamental issue is economic. With billions of dollars being spent by the government to purchase medical care, some form of review and audit is essential for accountability and good business procedures. The thrust of PSRO is to establish a local physician operated review mechanism with appropriate feedback to assure adherence to and implementation of appropriate standards for medical care. In this process medicine can in part control its own destiny in utilization of governmental resources in fulfillment of its broad mission. It can also become hopelessly enmeshed in bureaucracy.

As the authority for wage and price controls is due to expire on April 30, 1974, the Administration has introduced into the Congress a Bill which proposes elimination of controls and a free market for all *except* the health industry. This Bill (S. 3032) represents the greatest threat ever to the continuation of voluntary non-profit hospitals. In this Bill the President has asked for unqualified and complete authority to control wages, prices and even aggregate expenditures in the health industry until January 1, 1976. The Bill not only places hospitals totally under federal control, but places them under the direct and unfettered control of the President and his advisors. The Bill gives the President power in the broadest possible terms without any constraints. It is the assumption of complete dictatorial power over all aspects of the health field. This Bill is, and of a right ought to be, unconstitutional. In my opinion, it has closer resemblance to *ein Ausrufung* sent to the Reichstag about 1936 by Adolf Hitler than to a proposal for law in the Congress of the United States. Fortunately, the Senate's Banking Committee and the House Committee on Banking and Currency have recently voted to table all proposals relating to continuation of federal wage and price controls and further consideration of the proposed Bill is deemed unlikely.

The President and his advisors apparently view these proposed controls merely as temporizing measures until the administration's Comprehensive Health Insurance Plan (CHIP) can be enacted into law. The latter has been recently proposed by Senator Packwood (S 2970) and Representatives Mills and Schneebeli (HR 12684). It is one of the most recent of the seven Bills which have been introduced into the Congress designed to establish national health insurance. According to the President, CHIP is organized around seven principles: 1) comprehensive health insurance benefits; 2) costs to individuals based upon their ability to pay; 3) the strengths and diversity of public and private financing systems; 4) public funds to be used only where needed and allegedly no new federal taxes to be required; 5) freedom of choice by patients and no direct federal payments to physicians; 6) more effective use of health resources encouraged; and 7) consumers, providers, insurors and government would have a direct stake in making the system work.

The proposed program is estimated to cost six billion dollars per year and will require employers to provide basic approved health insurance coverage as well as health maintenance organizations (HMO) for all full time employees. This participation, however, is voluntary at the option of the employee. In summary, CHIP is voluntary, comprehensive health insurance provided through current systems for all who wish to enroll. It is allegedly designed to preserve our present health insurance and medical system.

Already critics are chipping away at CHIP. Senator Edward Kennedy is especially critical of its dependence on private insurance carriers. In addition, other opponents complain that the plan will cost consumers more than they pay for health care now or would pay under an outright federal-pay plan.

Both the Nixon administration and Senator Kennedy and his laborite allies have expressed great expectations in the value of so-called HMO's as virtual panaceas in health care delivery. Their enthusiasm is hardly infectious. The Senator's Health Security Bill (S 3, H.R. 22–23) supported by Representative Martha Griffiths, proposes universal, comprehensive, compulsory, cradle-to-the-grave, health care based on radically changing our entire medical system to a socialistic structure financed by a huge system of taxation. The original fully developed Kennedy plan for national health insurance, according to his ardent critic, Mr. Nixon, would have a price tag of $80 to $100 billion per year. To quote Ronald Reagan, "that's quite a lot of 'Teddy-care'."

Furthermore, the magnitude of the bureaucratic structure involved in administering the proposed Kennedy-Labor program simply boggles the mind. The degree of regimentation of both patients and physicians would be extreme. The financing and organizational emphasis would be based on prepaid group practice at the expense of traditional fee for service. The plan attempts to control costs by a system of regional health budgets with which this country has no experience.

It is not difficult to understand the ideological motivation of labor leaders and those left of labor in collectivizing health care in the United States. But it is incongruous that the young senator from Massachusetts be tarred with the same brush. The enactment of the Kennedy-Labor program would have catastrophic results for American physicians and their patients.

Apparently Mr. Kennedy agrees with this viewpoint since he has recently jettisoned his original labor-backed health insurance proposal to submit a compromise national health insurance plan to Congress in collaboration with Representative Wilbur Mills.

The Kennedy-Mills Bill (S. 3286, H.R. 13870) which took Washington by surprise a few weeks ago would provide benefits similar to, but somewhat more liberal than those contained in President Nixon's CHIP. The Kennedy-Mills Bill would be mandatory requiring participation and contribution from all persons. The new Bill provides for inpatient hospital services with no day or dollar limitation, physician's services and other medical services subject to an annual deductible of $150 and twenty-five per cent co-insurance. The maximum deductible per family would be $1,000 per year as opposed to $1500 under the Nixon plan. Practitioners would be free to participate in the program, but if they choose not, they could not provide services under the system. Premiums would be collected through the Social Security system and a new Social Security Board, reporting directly to the President, would direct the program. Existing health insurance carriers would be retained to collect co-insurance and deductibles, make disbursements, and administer the transaction of insurance claims. The sponsors of the Bill further anticipate that private carriers would continue to write insurance policies covering supplemental benefits.

The Bill also adopts the Administration's plan for a health credit card so that patients would be billed for co-insurance and deductibles after receiving care. The legislation would also establish a National Health Development Resources Board within HEW to be responsible for the delivery of health care services provided under the measure.

By lodging the proposed national health insurance firmly in Social Security and basing it on the Social Security payroll tax (the Kennedy-Mills plan is an extension of Medicare to the entire population) Representative Mills has moved skillfully to protect the flanks of his powerful Ways and Means Committee from a committee reorganization threat in the Congress. And Senator Kennedy and Labor have quickly compromised their Health Security position to seize this powerful com-

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petition against the Nixon administration's CHIP.

Among the other Bills in Congress proposed to provide national health insurance is the American Medical Association's "Medicredit." This is a voluntary income tax plan sponsored by Senator Vance Hartke of Indiana which partially offsets costs of private health insurance by means of tax credits. A qualified policy would offer comprehensive insurance against the ordinary and catastrophic expenses of illness. The government would pay all premiums for low income persons; individual and dependents with no income tax liability. For others, the government would pay between ten per cent and ninety-nine per cent based on family or individual income. It would pay everyone's premium for catastrophic expense insurance. Coverage would be provided through private health insurance. Enrollment in prepaid groups would be included. "Medicredit" has apparently more sponsors in the Congress than any other currently proposed health legislation.

Three additional plans for national health insurance are proposed by Representative Ullman in collaboration with the American Hospital Association, Senator McIntyre and Representative Burleson in cooperation with the Health Association of America and by Senators Long and Ribicoff who propose a new comprehensive national Medicaid plan with catastrophic health insurance.

A number of other national health insurance proposals are under serious consideration by various groups in and outside the Congress, including a task force of the American Association of Medical Colleges.

This incomplete catalog of current health legislation in the Congress has implications for American physicians, surgeons and their patients which are most ominous. It is obvious that the Congress is making a broad appraisal of national health insurance and is giving serious consideration to instituting sweeping changes in our medical care delivery system.

Why are these multiple socialistic, health legislative proposals filling the bins of congressional hoppers in the spring of 1974 in the United States of America? I would be very pleased if I could present a penetrating analysis of the societal and political thrusts which underlie them. I cannot do better than draw on the work of Harry Schwartz, the political analyst, who has written a superb book in defense of the American pluralistic medical system which provides a strong set of arguments against the socialization of medicine and the adoption of a uniform system of "free" medical care supported by taxes in this country. Let me quote from two paragraphs in his concluding chapter:

> ". . . the American Medical Care System with its four million workers, its more than 200 million patients and potential patients, its incredible array of specialized skills and equipment, and its billions of dollars of capital investment is quite simply the most complicated industry in the United States. To suppose that we know enough to improve it through radical changes imposed upon this system in a brief period is fantasy more appropriate to an LSD trip than to sober legislative deliberation."

A second conclusion of Mr. Schwartz is as follows:

> "We have argued above that the American Medical System is much better than is usually assumed, and we have warned against radical Krushchev-like sudden changes in this very complex mechanism. But none of this implies that American medicine is perfect, that the status quo must be preserved intact, or that improvement is impossible. Our plea here, rather, is for intelligent change applied where change is needed and will improve matters, for "patching up" and remedying the weaknesses of a basically sound mechanism, and for change at a pace that will permit the numerous interests involved—providers and consumers alike—to compromise their differences and work out mutually tolerable, if not always mutually ideal, compromises.
>
> "Reasonable critics of the American Medical System have centered their fire on two problems: 1) the high and rapidly increasing cost of medical care and 2) the difficulties of access to this care in some areas and for some population groups."

Mr. Schwartz has summed up our assets and our liabilities with his characteristic clarity and accuracy. He is well aware that we constitute the greatest profession in this great country, and that despite our magnificent achievements and our professional elitism, we have little professional unity and very poor organization of the way we handle our professional activities and our patients' problems at the national level, especially in regard to the socioeconomic and political aspects.

In the Congress there are men and women with varied motives; some are statesmen, most are not. All are politicians. All are responsible to their constituents. The Congressmen and through them their constituents have brought these national health insurance bills before the Congress. Our professional freedom and the most free and effective system of medical and surgical care in the world today are in jeopardy.

What can we do about this? What can the fellows of the American Surgical Association do about the plight in which we find ourselves?

Before attempting to outline answers in broad categories, let us look directly at ourselves. The American Surgical Association is the most venerable national surgical organization in the country. We have a tradition of professional elitism and a current concentration of talent which are unsurpassed by any similar professional organization in this nation. This talented leadership must be focused on the fundamental problems which need solving in national health care in order to forestall radical governmental restructuring of health care delivery in this country along the socialized lines of Sweden or Great Britain. These fundamental problems are those alluded to by Mr. Schwartz, specifically, the high and rapidly increasing cost of medical care and the difficulties of access to this care in some areas and for some population groups. Sound solutions for these extraordinarily profound problems must be based on professional achievement.

Several principles which are deeply rooted in America will guide our efforts to cope with the societal and political pressures which threaten our medical system: 1) allegiance to the free enterprise system upon which the national economy is founded; 2) the strongly American tendency to "plan for a rainy day" on which our private insurance industry is based; 3) the fee-for-service basis of most of American medical practice; 4) the free choice of physicians and of patients; and 5) the use of public funds to subsidize the health care of the poor. To these most physicians would add the use of public subsidy to defray catastrophic expenses of injury and illness.

There are two major avenues of attack on this conflict of professional freedom and governmental control which I should like to propose for adoption by the American Surgical Association:

First, let us put our professional house in order.

Second, let us take advantage of Article I of the Bill of Rights and "petition the government for a redress of grievances."

In elaboration of this first proposal to put our professional house in order, we clearly need to establish the machinery whereby the powerful suggestions made by Francis Moore in his presidential address to this Association two years ago can be implemented. You will recall that these recommendations included: 1) the validation of staff specialty credentials in the accreditation process in hospitals where surgery is performed; 2) the national monitoring and control of surgical specialists; and 3) the establishment of a national surgical placement service. Dr. Moore emphasized the importance of implementing these programs in the voluntary sector. The Study of the Surgical Services in the United States sponsored by the American College of Surgeons and the American Surgical Association has expended four years of active work. Dr. George Zuidema and his committee will present synopses of their work during this meeting. The data derived from this important study will serve as the basis for logical decision making by surgeons about surgeons and surgery in this country. Along with credentialling, continuing education, peer review, recertification and other criteria of fitness as a surgeon must combine to put our professional house in order. Implementation an action will require appropriate machinery. A conjoine committee of the ACS and ASA is clearly indicated.

In elaboration of the second proposal to "petition th government for a redress of grievances," the America Surgical Association needs to become an organization o political activists. Certainly not long-haired protestor but an organization of balding conservatives who hav an active participatory interest in politics and in legislation which affects its fellows' professional lives and freedoms. We have been aloof, superiorly patrician an naively lacking in political clout for 94 years!

Unlike the American College of Surgeons, the American Surgical Association has no tax problem which interferes with its giving testimony at congressional hearings, lobbying or using other means of currying favorabl political action in the grave health legislative matter which threaten us.

Our colleagues in the American Association of Medical Colleges have maintained an effectively activist monitor of federal health activities in the last few years an have repeatedly demonstrated the value of "petitionin the government for a redress of grievances." Their mos successful action to date, a suit against the Administration over impounded National Institutes of Health research funds, resulted in President Nixon ordering th release of approximately $1 billion in previously impounded fiscal 1973 funds for health and education That's not bad for a group of deans!

A friend of mine who works as a political observe with medical interests in Washington wrote recently "The continued division of the medical profession o important issues and the lack of sophisticated approac to members of Congress on medically related legislatio will continue to plague the profession. This lack of a coordinated unified front for or against legislation doesn' add to the hope for a reduction of bureaucratic interference in clinical or academic medicine."

These are wise words from a wise man. And we hav many wise men in this Association. Men who are wis enough to work well as political activists in a sophisticated and effective manner. They should be appointe to a Governmental Liaison Committee!

The American Surgical Association has primary concern for the betterment of medical and surgical care o patients in this country and not primary concern for it own welfare. We have deep concern that much of th health legislation currently proposed would, if enacted worsen the delivery of medical and surgical care i America and restrict the professional freedom of American physicians and surgeons.

In closing, let me thank you again for letting m serve as your President.

Ten Years Clinical Experience with Partial Ileal Bypass in Management of the Hyperlipidemias

HENRY BUCHWALD, M.D., Ph.D., RICHARD B. MOORE,M.D.,
RICHARD L. VARCO, M.D., Ph.D.

The first partial ileal bypass operation specifically for the reduction of plasma lipids was performed by us in 1963. Since then we have operated upon and followed for more than three months 126 hyperlipidemic patients. Clinical metabolic studies, before and after the procedure, have demonstrated a 60% decrease in cholesterol absorption, a 3.8-fold increase in total fecal steroid excretion, a 5.7-fold increase in cholesterol synthesis, a 3-fold increase in cholesterol turnover, and a one-third decrease in the miscible cholesterol pool. Circulating cholesterol levels have been lowered an average 41.1% from the preoperative but postdietary baseline. An average 53% cholesterol reduction has been achieved from a pretreatment baseline using a combination of dietary and surgical management. Plasma triglycerides have been reduced in primary hypertriglyceridemic patients (type IV) an average of 52.6% from their preoperative but postdietary baseline. One patient died in the hospital and there have been 13 late deaths over the past 10 years. Four cases of postoperative bowel obstruction required reoperation. Diarrhea following partial ileal bypass is, as a rule, transistory and not a significant problem. No appreciable weight loss results from partial ileal bypass, which is an obvious distinction from the results of the far more massive jejuno-ileal bypass procedure for obesity. We have not encountered hepatotoxic, lithogenic, or nephrolithiasis complications in our partial ileal bypass patients. Sixty-nine per cent of our patients with preoperative angina pectoris have postoperative improvement or total remission of this symptom complex. Serial appraisal of followup coronary arteriographic studies offers preliminary evidence for lesion regression. It is concluded that partial ileal bypass is the most effective means for lipid reduction available today; it is obligatory in its actions, safe, and associated with minimal side effects.

From University of Minnesota Hospitals, Minneapolis, Minnesota

Atherosclerosis, with its associated evolving consequences, represents the greatest health menace to adults in the United States today. The threat to life and well-being from this disease is greater during the decades after the age of 40 than from all other causes.

The retrospective[26] and prospective studies[11,13,14] of atherosclerotic risk incriminate the circulating cholesterol concentration as a prime risk variable in the etiology of atherogenesis. The lipid-atherosclerosis hypothesis postulates that the circulating cholesterol concentration acts as an exponential influence on the individual's potential for developing atherosclerosis. The converse—namely, that lipid lowering will reduce risk—remains as yet unproven. Our goal in the laboratory and in our clinical research has been to test the validity of the lipid hypothesis by the means of the partial ileal bypass operation, a technique designed for maximum reduction of plasma lipid levels. National trials of the lipid-atherosclerosis hypothesis, one utilizing partial ileal bypass, have been funded by the National Heart and Lung Institute and are currently underway.

Available data document that diet and current drug therapy, singly or in combination, only infrequently approach the lipid reduction feasible with partial ileal bypass.[8] Negative aspects of treatment with diet and drugs have been the failure of cholesterol lowering in a significant percentage of patients,[18,28,31] response escape,[24] and rebound of lipid levels.[30,31] In our experience, partial ileal bypass has never failed to lower lipid levels, and has never been associated with either response escape or rebound of lipid levels. Patients can elect to adhere con-

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sistently, intermittently, or not at all to a diet or a drug protocol, but the therapeutic effects of bypass surgery are obligatory and reversible only by operation. If a clinical decision is made to attempt the lowering of an individual's lipids, three rational and primary therapeutic alternatives, singly or in combination, are currently available: diet, drug and partial ileal bypass surgery.

This paper summarizes our clinical experience with the partial ileal bypass operation over a ten year period beginning in May 1963. The laboratory and clinical work of other investigators, as well as our own animal studies, are not reviewed; that has been done by us elsewhere.[8]

Partial ileal bypass differs substantially from jejunoileal bypass. The jejuno-ileal bypass operation, in which the proximal 40 cm of jejunum are anastomosed to the distal 4 cm of ileum, attempts alleviation of morbid exogenous obesity. With better than 90% of the small intestine bypassed, the therapeutic goal is weight loss. Lipid reduction is a valuable and accompanying benefit. The jejuno-ileal bypass usually produces diarrhea, can induce serious electrolyte imbalance, and has been associated with hair loss, arthritis, nephrolithiasis and liver failure. Partial ileal bypass short-circuits only the distal 200 cm of small intestine, or one-third the small intestinal length, whichever is longer.[8] Our data show that partial ileal bypass, though associated with diarrhea at times, is not responsible for the problems mentioned above. We would like to emphasize the fact that partial ileal bypass management does not cause significant weight reduction.

Metabolic Studies and Cholesterol Dynamics

The original postulate[6] of our intestinal bypass procedure had two propositions: 1) The small bowel bypass should permanently interfere with the entero-hepatic cholesterol cycle and 2) similarly influence the entero-hepatic bile acid cycle. We reasoned that partial ileal bypass would decrease cholesterol absorption and increase cholesterol and bile acid excretion, changes which would accelerate cholesterol turnover and increase cholesterol synthesis sufficiently to replenish the bile acid pool and to meet other body needs. We were interested in ascertaining to what level homeostatic equilibration would allow the circulating cholesterol concentration to fall; and, as a corollary, what overall effect these dynamics would exert on the miscible body cholesterol pool. We have developed metabolic methods for answering these speculations raised by the possibility of employing the partial ileal bypass procedure. We believe that a brief review of these techniques and the test results we obtained are germane to a sound understanding of the bypass operation.

Cholesterol Absorption

In 1963 we published a method of measuring the cholesterol absorptive capacity of the gut by determination of blood radioactivity following a standard oral test dc of cholesterol-4-C^{-14} in butter.[6] By plotting the circul ing radioactivity for four days we were able to obtain index of cholesterol absorption from the average blo radioactivity over the four days, or the peak blood rad activity response, or the area under the four day blo radioactivity curve. In 30 patients studied before, a three months after, partial ileal bypass, the choleste absorption was reduced an average of 60% (range 57% 95%).[7,9,10,37] We have retested this reduction in chol terol absorption in certain of these 30 patients repe tively, and we have no evidence of any trend reestablishment of their preoperative cholesterol absor tive capacity. Cholesterol absorptive adaptation by t functioning small intestine apparently does not occ and the effect of ileal bypass on cholesterol absorpti appears to be permanent.

Fecal Steroid Excretion

Fecal steroid excretion has been measured in select patients before and after partial ileal bypass using isotope balance technique.[36] The total fecal steroid e cretion rate in three patients before surgery averag 785 mg/day, which was somewhat lower than we h observed in normal subjects using similar techniqu (966 mg/day); however, their proportion of bile aci (49%) was the same as in the normals. Two months aft operation there was a 3.8-fold increase in total fec steroid excretion (from 785 to 2,955 mg/day), with much greater increase in bile acids (4.9-fold, from 3 to 1,934 mg/day) than in neutral steroids (2.7-fold, fro 386 to 1,022 mg/day). Similar magnitudes of fecal ste oid excretion were observed in two additional patien studied at one year after partial ileal bypass (4,295 a 2,246 mg/day), demonstrating the apparently permane effect of ileal bypass on fecal steroid excretion.[36,37]

Cholesterol Synthesis Studies

During the past several years we have used an *in vi* method for estimating cholesterol biosynthesis based the incorporation of tritium from body water into t plasma cholesterol.[37] We have determined choleste synthesis in 15 patients before and three months aft operation, and again at one year in six of these patien This index of cholesterol biosynthesis significantly i creased ($p < 0.001$) following partial ileal bypass: t 24-hour incorporation values averaged 0.0149 ± 0.00 before and 0.0855 ± 0.0301 three months after operatio The magnitude of the synthesis response was marked each patient, and the average group synthesis was i creased 5.7-fold. The six patients restudied up to o year had average values for the 24-hour incorporati ratio of 0.0145 before, 0.0877 three months after, an 0.0861 one year after operation.[7,37] Thus, increased ch lesterol synthesis appears to be maintained following partial ileal bypass.

Cholesterol Turnover Rate Estimation

We studied the isotopic cholesterol turnover rate in seven partial ileal bypass patients prior to operation and over four months following the procedure.[7,36,37] The specific activity curves of these individuals before bypass became log-linear after about 30 days. Following operation there was a more rapid rate of decline in specific activity values, which again became log-linear after about three weeks but with greater negative slopes (average half-time of 36.1 days compared to 68.0 days before operation). Three patients were restudied one year after operation when a second injection of labelled cholesterol was given. The second curves showed a more rapid decline in specific activity values and the log-linear portions were steeper than in the preoperative studies (half-time average 23.4 days compared to 30.2 days in the same patients before operation). These qualitative changes suggest that partial ileal bypass results in a marked and persistent increase in cholesterol turnover.

Mathematical analyses of the serum cholesterol specific activity curves were made using a two compartment open mammillary system as a model to describe the behavior of the labelled cholesterol.[33,36] In the seven patients studied preoperatively, the calculcated turnover rate averaged 930 mg/day. In the three patients who had repeat studies at one year the turnover rate averaged 2,840 mg/day, indicative of an approximate 3-fold increase.

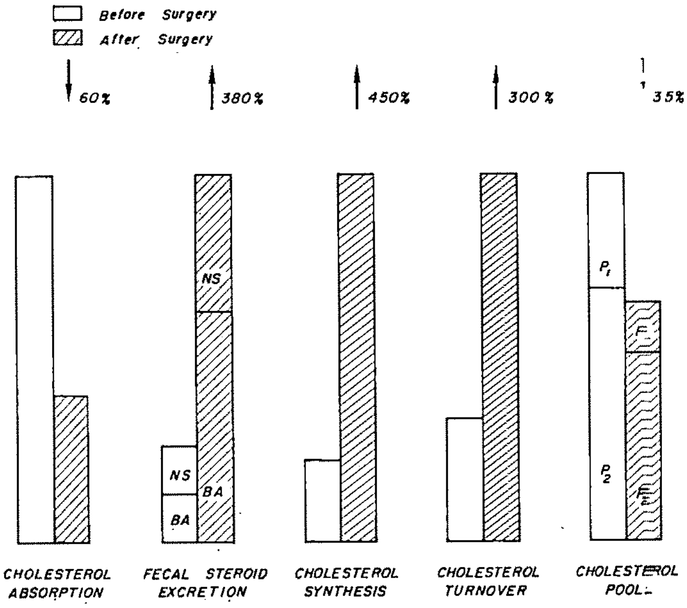

FIG. 1. Summary of cholesterol dynamics: NS = neutral steroids, BA = bile acids, P_1 = freely miscible cholesterol pool, and P_2 = slowly miscible cholesterol pool. (From Buchwald, H., Moore, R. B. and Varco, R. L.: "Surgical Treatment of Hyperlipidemia," Circulation Supplement, XLIX, May 1974, by permission of The American Heart Association, Inc.)

Cholesterol Pool Size Estimation

Using a method similar to that of Goodman and Noble[21] we calculated the freely miscible (plasma, red blood cell, intestinal mucosa, liver), slowly miscible (muscle, subcutaneous depot fat, organ, arterial), and total (freely miscible plus slowly miscible) exchangeable cholesterol pools in three patients before and one year after partial ileal bypass.[36,37] Both the freely miscible and the total exchangeable cholesterol pools were higher in these subjects than comparable values we determined in normal subjects using the identical method (34.5 g and 83.0 g for the hypercholesterolemic subjects, 21.9 g and 69.2 g for the normals). One year after operation there was a marked reduction in the exchangeable cholesterol pools in the three bypass patients: the freely miscible pool averaged 34.74 g preoperatively and 28.21 g postoperatively, the slowly miscible pool averaged 48.73 g preoperatively and 26.27 g postoperatively, and the total exchangeable pool averaged 82.96 g preoperatively and 54.48 g postoperatively. In each patient there was a relatively greater reduction in the slowly miscible cholesterol pool than in the freely miscible cholesterol pool, suggesting a loss of cholesterol from tissues other than the blood and the liver, possibly from the arteries.

Figure 1 summarizes the changes in the cholesterol dynamics outlined above. To this writing, the basis for the triglyceride-lowering effect of the bypass operation has not been scientifically evaluated.

Effect on Plasma Lipids

Cholesterol Concentration

Although the plasma cholesterol concentration measures only a part of the freely miscible cholesterol pool and a small percentage of the total exchangeable pool, it is, nevertheless, indicative of body cholesterol balance. The plasma cholesterol is also the cholesterol environment of the arteries and the cholesterol site most accessible to measurement.

No patient was considered for operation until he had completed at least three months on a dietary program tailored for his hyperlipidemia type.[38] Thus, the cholesterol levels given as the preoperative baseline values represent the mean post-dietary cholesterol concentrations. Surgery was effective in all patients, whether they had a good, poor, or no response to diet (and, in many, drug) therapy. All plasma cholesterol values are the mean values of three consecutive cholesterol concentrations.

To this time 135 individuals have undergone partial ileal bypass for hyperlipidemia at the University of Minnesota (88 males and 47 females). The age range for these patients is seven to 63, with a decade distribution of: first, 1; second, 13; third, 12; fourth, 23; fifth, 51; sixth, 33; and seventh, 2. Two deaths occurred prior to the scheduled three month postoperative evaluation and seven individuals have been lost to followup; thus, our data are based on 126 patients.

Table 1 gives the number of patients in each followup time interval, their mean preoperative and postoperative cholesterol concentration with standard deviation and standard error, and the average interval cholesterol reduction. These figures are paired analyses; if a time-interval value was not obtained for a patient, that patient's preoperative cholesterol concentration was omitted from the calculation of the mean preoperative cholesterol for that particular time period. These data are presented through the ninth year, since for accurate statistical analysis an insufficient number of individuals have been followed for ten years. Our three homozygous type II patients are excluded from Table 1 and are discussed separately in this section.

The mean cholesterol concentrations for each of the time intervals are plotted on Fig. 2. It is evident that the partial ileal bypass effect on the plasma cholesterol level is constant and lasting. Utilizing non-paired analysis and interval comparison to the total group preoperative cholesterol concentration (excluding the three homozygotes), an average 41.1% cholesterol lowering is achieved over the nine years.

We have one patient with a preoperative cholesterol value of less than 200 mg%; 46 of 90 (51%) of the heterozygous patients with a recorded one year postoperative cholesterol value had cholesterol levels lower than 200 mg%. There were 17 patients with plasma cholesterol levels below 250 mg% before operation; at one year 74 of the 90 (82%) of the patients had cholesterol concentrations below 250 mg%.

The magnitude of the one year postoperative plasma cholesterol reduction is shown as a frequency distribution bar graph in Fig. 3. These values range from a low of 5% in one patient to a high of 79% in another. Fou patients had responses of 10% or less and five had re ductions greater than 60%. Ninety-five of 114 (83%) ha cholesterol reductions of greater than 25%, 84 of 11 (74%) exceeded 30%, 74 of 114 (65%) exceeded 35%, an nearly half, 53 of 114 (47%), had reductions of greate than 40%.

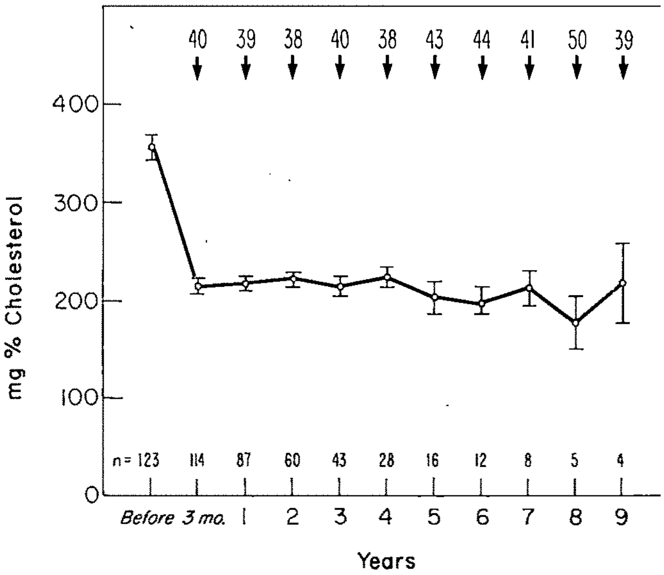

FIG. 2. Average plasma cholesterol concentrations before and afte operation (± 1 SE), excluding the three homozygous type I patients; number of patients at each time interval given.

For the three homozygous type II patients, the pre operative cholesterol values were 404, 577, and 919 mg% Their respective postoperative average reductions wer 13, 21, and 20%.

Twenty-four of our type II heterozygous patients wer on no therapeutic regimen when first seen by us. W treated them vigorously with a diet containing less tha 30% of total calories as fat, a polyunsaturated:saturate fat distribution ratio of 1.5, and total cholesterol conten less than 300 mg daily. Three months after dietary the apy, this cohort had a mean cholesterol lowering of 11 (423 to 376 mg%); only 16 of the 24 patients demor

TABLE 1. *Pre- and Postoperative Cholesterol Concentrations by Time Interval Group*

Time Interval	N	$\bar{x}$ Preop Cholesterol	SD	SE	$\bar{x}$ Postop Cholesterol	SD	SE	% Reduction
3 month	114	359	122	11	214	70	7	−40.3
1 year	87	357	125	13	217	68	7	−39.3
2 year	60	355	122	16	221	54	7	−37.9
3 year	43	358	128	20	215	56	9	−39.9
4 year	28	371	135	25	222	64	12	−40.1
5 year	16	328	100	25	202	71	18	−38.3
6 year	12	301	49	14	199	40	12	−33.8
7 year	8	320	97	34	212	47	17	−33.8
8 year	5	290	31	14	177	60	27	−38.9
9 year	4	357	133	66	219	79	40	−38.7

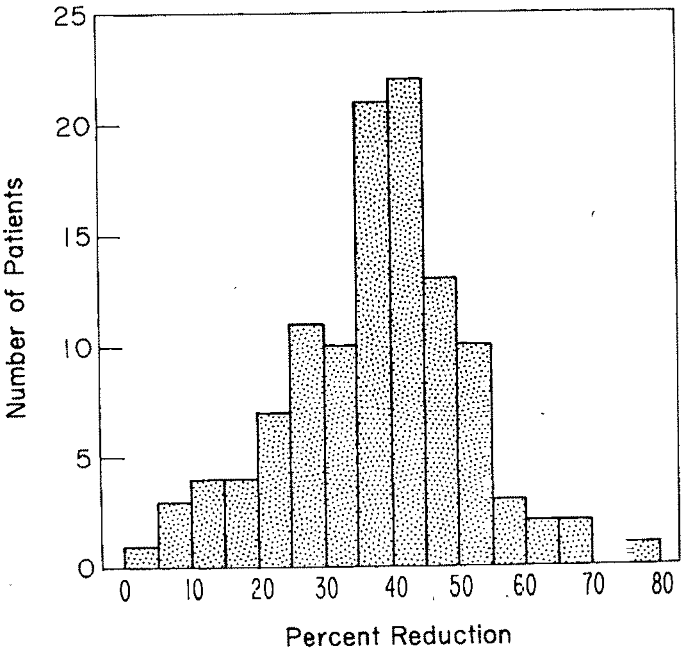

FIG. 3. Frequency distribution of one year postoperative percent reduction in plasma cholesterol levels.

strated a measurable decrease in their plasma cholesterol concentration. Three months following partial ileal bypass, the average plasma cholesterol level for this group was 224 mg%, representing an additional 42% plasma cholesterol level reduction and an overall cholesterol lowering of 53%. Therefore, good dietary adherence in combination with a partial ileal bypass can achieve a halving of the cholesterol concentration.

Using the Fredrickson[19] and the revised Fredrickson[3] classification, and employing the term "mixed type" for those individuals with electrophoretic staining patterns characteristic for both types II and IV, we have analyzed the post-bypass effect on the circulating cholesterol level by lipoprotein type. We have designated as type IIX those individuals with a known preoperative hypercholesterolemia but with no recorded preoperative triglyceride concentration (patients operated upon prior to publication of the Fredrickson classification system). The average reductions, at one year following operation in plasma cholesterol from the post-dietary preoperative baseline values were: type IIX–32.0%, type IIA–34.8%, type IIB–41.3%, type III–47.5%, type IV–45.6% and mixed type–41.1%. These data are graphically represented in Fig. 4.

Triglyceride Concentration

Our triglyceride data are not as extensive as our cholesterol data; nevertheless, the dramatic changes in the triglyceride concentration are well documented. Table 2 gives the data on triglyceride changes for eight years and employs the same paired analyses format utilized in the presentation of the cholesterol figures.

A more cogent appreciation of the triglyceride lowering effect of partial ileal bypass surgery can be obtained by an evaluation based on the preoperative lipoprotein typing (Fig. 5). The 17 type IV patients, all with markedly elevated preoperative plasma triglyceride levels, sustained an average 52.6% reduction at one year after operation (1127 to 534 mg%). The response of the "mixed type" hyperlipoproteinemic patients (n = 5) was −16.5% at one year (491 to 410 mg%). The 37 type IIB patients, those individuals with a hypertriglyceridemia accompanying their hypercholesterolemia, had an average lowering of the circulating triglyceride concentration at one year of 16.7% (257 to 214 mg%). On the other hand, in the 49 IIA patients(those hypercholesterolemic individuals with low or normal preoperative triglyceride concentrations, there was a paradoxical average increase in the triglyceride level at one year of 21.1% (117 to 142 mg%). Nevertheless, despite the increase, the average triglyceride level remained within the accepted range of normal. At the present time, we do not have a satisfactory explanation for this phenomenon in the type IIA patients; we assume that it may be related to the bile acid loss, since a similar finding has been reported following the use of cholestyramine by Grundy.[22]

Clinical Evaluation

Patient Selection

Of the 135 patients in this series, 104 (77%) had preoperative evidence of coronary heart disease by history

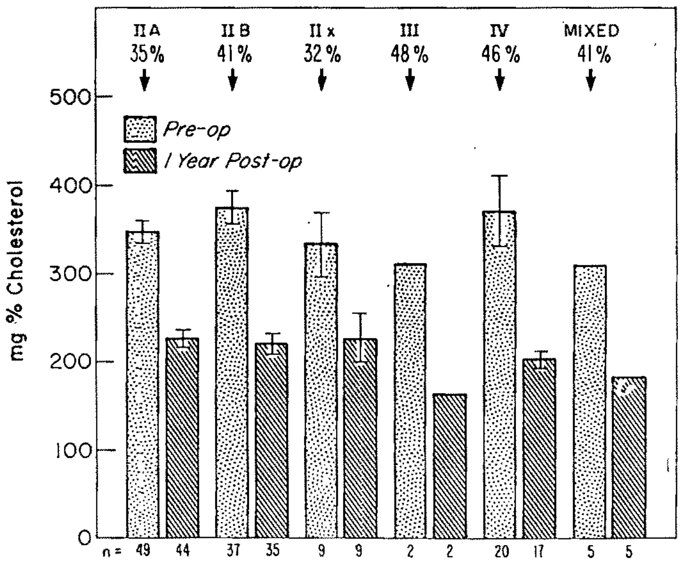

FIG. 4. Average one year postoperative plasma cholesterol level response by lipoprotein type (± 1 SE); type IIX = no triglyceride values before operation.

TABLE 2. *Pre- and Postoperative Triglyceride Concentrations by Time Interval Group*

Time Interval	N	$\bar{x}$ Preop Triglycerides	SD	SE	$\bar{x}$ Postop Triglycerides	SD	SE	% Reducti
3 month	98	355	760	77	224	158	16	−36.7
1 year	73	385	876	102	244	215	25	−36.7
2 year	47	465	1080	158	237	175	26	−49.1
3 year	31	636	1304	234	286	247	44	−55.0
4 year	17	649	1694	411	243	141	34	−62.6
5 year	10	523	650	206	296	223	71	−43.4
6 year	4	223	84	42	183	52	26	−19.8
7 year	2	224	38	27	157	12	8	−30.1
8 year	2	258	86	60	162	16	11	−37.3

or electrocardiography or arteriography. The other 31 individuals (23%) underwent bypass surgery exclusively for the criteria of hyperlipidemia and a family history of early atherosclerotic disease. With rare exceptions we have limited the operation to those patients under the age of 60 and with no evidence of cardiac failure. We have operated upon nine pre-pubertal children, the youngest of whom was seven years old at the time of operation.

Mortality and Morbidity

To this time, we have had only one immediate postoperative death for an in-hospital mortality of 0.7%. This patient had sustained three myocardial infarctions prior to his bypass and he died on the fourth postoperative day from his fourth infarction. There have been 13 late deaths, from two to 90 months after bypass. All, except two, have been due to an acute myocardial infarction; one died of a cerebral vascular accident and the other of acute infectious hepatitis. Late postoperative morbidity has been limited to four cases of bowel obstruction that necessitated operative intervention. Immediate in-hospital complications have consisted of rare and minor wound problems, none of which prolonged hospitalization.

Side Effects

Diarrhea is the one annoying side effect of this operation; however, it is not a significant or persistent problem in the majority of patients. On the basis of a patient survey taken one year after partial ileal bypass, 86% of our patients had less than five bowel movements daily, without the aid of bowel-controlling medications. Within one to two years, better than 90% of the patients experienced an increase in firmness and consistency of the stools. One patient, however, underwent operative restoration of bowel continuity elsewhere because of intractable diarrhea.

Since the distal ileum is bypassed, we have always instructed our patients to receive 1,000 μg of vitamin B_{12} intramuscularly every two months for the rest of their lives. Nygaard and coworkers[39] first noted the interesting phenomenon of a significant recovery in B_{12} absorpt between three to 12 months after the operation. We cently have also noted a return of B_{12} absorptive capa ten years after bypass in certain individuals with a n mal preoperative B_{12} absorption test (Schilling test) a essentially no B_{12} absorption demonstrated one y following the bypass procedure (unpublished data)

As previously stated, the partial ileal bypass, unl the jejuno-ileal bypass, is not associated with nutri malabsorption or significant weight loss. Neither is partial bypass complicated by liver damage, establi ment of a lithogenic bile, arthritic changes or associa nephrolithiasis.

Angina Pectoris and Arteriographic Changes

Through personal interviews, we have documen the clinical course of angina pectoris in 94 patients. Nc

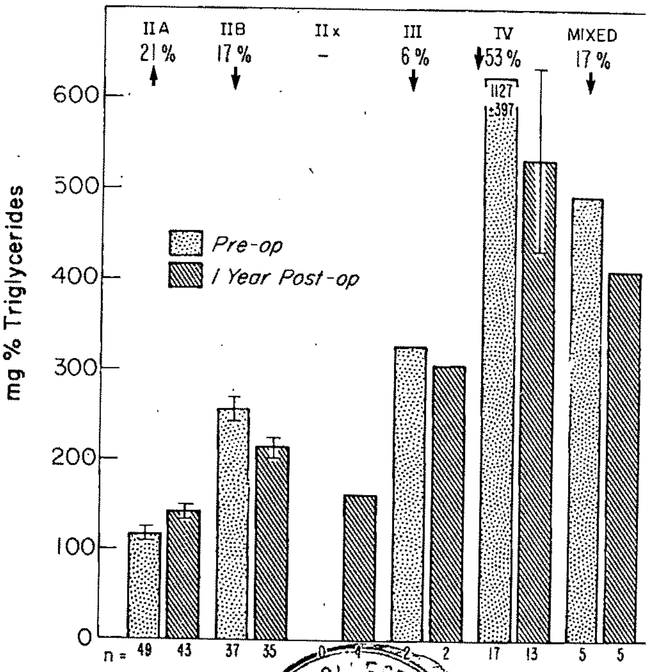

FIG. 5. Average one year postoperative plasma triglyceride le response by lipoprotein type (± 1 SE); type IIX = no trigl eride values before operation.

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of the 39 individuals who were angina pectoris negative prior to operation developed these symptoms subsequently. Of the 55 preoperative angina pectoris positive patients, 7% stated that they were worse, 24% had no change, 25% reported moderate improvement as determined by a reduction in their use of nitroglycerine, 18% stated that they had marked improvement as determined by their reduced use of nitroglycerine and a significant increase in exercise capacity, and 26% stated that they had complete remission of angina and were able to carry out increased activity. Thus, 69% of the patients with angina pectoris present prior to operation experienced some degree of improvement. Certainly, autopersuasion can and has played a significant role in the reported severity of this particular subjective phenomenon. We have, however, reported on an *in vitro* experiment utilizing rabbit blood, in which we demonstrated an oxygen diffusion block from red blood cells with a high membrane cholesterol content.[46] In some of our patients there has been an improvement in the time and grade controlled treadmill exercise electrocardiogram in association with their postoperative reduction in angina symptoms; however, this finding has not been consistent.

Our radiologists have previously reported[2,27] an apparent regression of atherosclerotic plaques, as demonstrated by serial arteriographic studies, in three partial ileal bypass patients. Non-progression of disease was found in 12 of 22 (55%) additional patients with technically comparable preoperative and postoperative (at least two years) arteriograms. Confirmation of this attempt at hard serial evaluation of atherosclerotic plaque changes in a controlled population study is necessary.

Discussion

Our clinical findings in regard to lowering of cholesterol and triglyceride levels, the limited nature of the postoperative diarrhea, and the diminution in angina pectoris symptoms have been confirmed by other investigators.[*,12,20,23,32,34,42,48,49] Balfour and Kim[1] recently reported better results in two homozygous type II children than we have achieved in the homozygous population. They report a 42% and a 33% sustained cholesterol reduction for greater than three years.

When a clinician evaluates options of therapy, he must weigh the apparent advantages against the risks. We have shown that partial ileal bypass offers advantages of maximum and obligatory effectiveness, no response escape, and safety. We have also enumerated the risks and side effects involved in managing the partial ileal bypass patient. In our review[8] of the best available publications on dietary lowering of cholesterol levels, we concluded that the mean cholesterol reduction obtainable by diet was 6% net; i.e. subtracting the 6% cholesterol reduction sustained by the control groups in these publications from the gross test group mean reduction of 12% leaves 6%. Mean reductions of cholesterol levels, obtained from the literature for the more common drugs utilized in hyperlipidemia management, include 22% for cholestyramine, about 15–20% for clofibrate, and 23% for nicotinic acid.[8] Hunninghake[24] has clearly pointed out effect escape with clofibrate and Levy and coworkers[31] have demonstrated lipid level rebound after discontinuation of clofibrate management.

Cholestyramine is not absorbed from the gut and no systemic side effects have been reported with its use; its bile acid binding action, however characteristically causes constipation when the resin is given in effective therapeutic dosage. To date, this powdered substance is available only for suspension in a liquid media and it is described as poor in flavor by the majority of its users. The precise metabolic site or sites of action of clofibrate have not been established. While clofibrate side effects are few, abnormal liver function[50] and myositis[20] have developed in association with its use. The manufacturer warns that clofibrate can potentiate coumadin anticoagulants and causes nausea in 5% of individuals on this medication. Nicotinic acid activity on the body lipids is also not fully understood. The use of nicotinic acid has been limited by its predictable and rather potent side effects. Flushing of the skin occurs initially in nearly all patients started on therapy and persists in 10 to 15% of individuals.[16] Other known side effects of nicotinic acid include erythematous rash, pruritis, hyperpigmentation, gastrointestinal disturbances, hyperglycemia, postural hypotension and the more serious reactions of hyperuricemia and impairment of liver function, including jaundice.[4,15,16,40]

New drugs are continuously being proposed for the management of the hyperlipidemias. We must be wary of these new agents until all their actions are well documented over a period of several years. The late and disastrous experience with MER-29, which was never fully documented in the scientific literature by its early advocates, is a reminder to the physician of the consequences of haste. Estrogen therapy also has been abandoned; it caused feminization in men,[41] intravascular clotting,[25] and its use was associated with an increased frequency of sudden death.[45] Though the early reports on the use of dextrothyroxine were promising, the side effects of this agent have mitigated against its greater usage. Dextrothyroxine can potentiate angina pectoris and arrhythmias, produce hypermetabolism and even bring about functional hyperthyroidism.[5,16,17,35,47] Indeed, because of these actions, the code in the Coronary Drug Trial was

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[*] Morgan F., Moore F. B.: personal communication and Streeter M : personal communication.

broken for dextrothyroxine and the drug was removed from the trial protocol.[43,44]

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Discussion

Dr. Thomas Earl Starzl (Denver): This paper is part of a landmark accomplishment of the Minnesota group, whereby they have influenced lipid metabolism by changing the intestinal continuity, and which work has been supported by the brilliant studies of Scott and his associates from Vanderbilt.

An alternative approach, and one by no means as standardized in its indications, is portacaval shunt—simple end-to-side portacaval shunt. You may remember from our last year's presentation the profound lowering of the secondary hyperlipidemia of glycogen storage disease after end-to-side portacaval shunt.

(Slide) We have also done end-to-side portacaval shunt in this child, who had the lethal syndrome of Type II primary homozygous hyperlipidemia, or idiopathic hypercholesterolemia, which has been generally conceded to be relatively refractory to the Buchwald-Varco bypass.

This child had a nearly lethal myocardial infarction by the time she was 11 years old, apparently from deposition of these kinds of xanthomata in her coronary arteries, from which mechanism she also had aortic stenosis with a gradient of 60 mm Hg.

(Slide) After an end-to-side portacaval shunt, there was this spectacular lysis of cholesterol from very nearly 1000 mg % on a low, or no cholesterol diet, to a level which has fallen to normal. Her continuous angina pectoris ceased; her heart failure slowly regressed; and the aortic murmur gradually receded in the followup period, now more than 14 months, and without any side effects from the portacaval shunt.

What is the mechanism of this really astonishing effect? (Slide) Here is a dog experiment which selectively diverts intestinal nutrients around the liver, shown here under B, by this anastomosis at this level, with ligation of the superior mesenteric vein here. Later—usually six or eight weeks later—a second stage can be done by performing a high portacaval shunt. The upper splanchnic organs are thereby drained around the liver. This second stage of course is primarily a diversion of hormones—rich blood from the pancreas and other upper sylanchnic organs.

(Slide) This kind of result is essentially always obtained in dogs and, we think also, in baboons, on the basis of two baboons we have studied. The mesenteric bypass has had no lasting effect on the serum cholesterol levels of these dogs; whereas when the pancreatic hormones are shunted at the time of the second stage procedure, there is a fall in the cholesterol, which starts down rather soon and is maintained. Thus we think the lipid lowering effect of portacaval shunt is from the shunting of hormones, particularly the insulin-glucagon combination.

I want to emphasize our really conservative attitude about portacaval shunts for this indication, because of the potentially devastating side effects of portacaval shunt. We did one case 14 months ago, and have not done a second one since. With this long a followup we will now go ahead with more cases.

Dr. William V. McDermott (Boston): These data presented by Dr. Buchwald and Dr. Varco and their associates over the years led us to consider this procedure in another relatively rare group of patients, those with intractable pruritus from a variety of causes, whether primary biliary cirrhosis, secondary uncorrectable biliary cirrhosis, giant cell hepatitis, and others.

Most of these patients either have such a poor prognosis, or the pruritus is controllable through cholestyramine or external biliary drainage. Only rarely will the appropriate patient appear; but the theory of correcting the distressing symptoms through this particular procedure seems borne out in the one instance where we did have what we felt was an appropriate case, a young boy with giant cell hepatitis, uncontrollable in any other way, and who did respond dramatically in terms of correction of his symptoms from the utilization of this procedure.

I only suggest that this is appropriate theoretically, and may be practically useful in the occasional patient with this particular set of criteria.

Dr. Richard R. Lower (Richmond): Dr. Buchwald has presented a very favorable comparison with preoperative diet. I wonder if he has any comments about comparisons of surgery with drug therapy.

Dr. Henry Buchwald (Closing discussion): Recently, we had the privilege to review diet and drug therapy of the hyperlipidemias. In addressing ourselves to this task, we reviewed the best published data. To give you some general figures, the net cholesterol reduction by dietary management, if you subtract the reduction obtained in the control groups, has been approximately 6–7%. The cholesterol lowering from drug therapy has, at best, been in the 25–30% range. Furthermore, there are no uniformly effective drug agents; drug effect escape and rebound of lipid levels after discontinuation of drug therapy have been documented. It is also unrealistic to expect lifelong adherence to a strict dietary protocol or a regimen of expensive drugs, especially by younger and asymptomatic individuals.

Balfour and Kim have recently reported on two homozygous children in whom they have achieved better results than we have with the partial ileal bypass in our one homozygous child. Certainly, from the currently available clinically proven armamentarium, the partial ileal bypass procedure has shown the best and the most lasting cholesterol reduction in this, fortunately small, sub-group of the Type II lipid abnormality.

Dr. Starzl has brilliantly applied his knowledge of the liver and portacaval shunting to the management of a child with homozygous type II hyperlipoproteinemia. We are certain that he will follow up on this report with extensive animal studies and a carefully monitored clinical trial.

In the future a spectrum of operations may become available in the treatment of hyperlipidemia and atherosclerosis. For example, partial ileal bypass, a technically simple operation, could become the procedure of choice for certain hyperlipidemic individuals. Other procedures may be optimal in the management of different hyperlipidemic patients.

The Role of Surgery and Hyperalimentation in Therapy c Gastrointestinal-Cutaneous Fistula

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CLAUDE E. WELCH, M.I

Thirty-eight patients with external gastrointestinal fistulas arising from different levels of the gastrointestinal tract, observed and treated at the Massachusetts General Hospital, from December 1970 to April 1973, are analyzed. Surgical complications were the causes of fistulization in 77% of the cases. The treatment program included parenteral nutrition through a subclavian line in all cases. The 38 patients were fed parenterally for a total of 2311 days. Spontaneous fistula closure occurred in only 11 of the 38 patients. Surgical procedures were necessary in 71.05% of the cases to control fistula complications or persistent fistula drainage. Operative success rate was 70.4%. Parenteral nutrition effects on metabolic parameters, fistula secretion, nutritional status, morbidity and mortality of fistulas are discussed. Parenteral nutrition hazards are also presented. Overall mortality in this series was 21%. Roles of parenteral nutrition and surgery in the total management of external gastrointestinal fistulas are suggested.

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ALL PREVIOUS REPORTS on the management of gastrointestinal-cutaneous fistulae have demonstrated the gravity of this condition with overall mortalities in different levels of the gastrointestinal tract ranging from 20% to 62%. Treatment in the past has generally consisted of conservative measures, followed, in case of failure, by surgical attack on the fistulae in an attempt to stabilize the precarious metabolic and nutritional state of these patients.[1,3,5,7,8,10] The introduction and standardization of parenteral nutrition[2,4,6,10] has improved considerably the treatment and prognosis of patients with gastrointestinal-cutaneous fistulae, since prior studies suggested that malnutrition and electrolyte imbalance were among the main causes of death.[1,3,8,12]

In 1960, a previous report from this institution placed the mortality range for external gastrointestinal fistul between 16% in colonic fistulae and 62% in gastroduod nal fistulae.[3]

It has been our impression that since the introductic of total parenteral nutrition, the mortality in gastroi testinal fistulae in this hospital over the past three yea has decreased remarkably. To be sure, not all of tl decrease in mortality has been due to total parenter nutrition, for there have been other advances in tot patient care since the early 1960's. Recently, McPhayde and Dudrick[6] reported a series of 62 patients with i ternal and external gastrointestinal fistulae treated wi hyperalimentation, obtaining spontaneous fistula closu in 70.5% with an overall mortality as low as 6.45%. O experience suggests that spontaneous closure is less cor mon, particularly in the presence of certain featur which we have attempted to identify systematicall such as lack of continuity of bowel, presence of intr abdominal abscesses, and distal obstruction which ter to point to operation as the only means of obtainir closure of these fistulae. This report represents an o going study of patients with gastrointestinal-cutaneo fistulae in this institution and is at variance with tl paper of McPhayden and Dudrick perhaps because an apparently different patient population.

Since 1970, when the Hyperalimentation Unit at tl Massachusetts General Hospital was formalized, unt April of 1973, 38 patients with external gastrointestin fistulae have been treated on the Surgical Services. Tot parenteral nutrition has been an integral part of the treatment program. In most cases total parenteral n

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Reprint requests: Josef E. Fischer, M.D.

trition of long duration was maintained prior to and after surgery. The following study will attempt to document the respective roles of hyperalimentation and operative surgery in the therapy of these important complications.

Clinical Material

Thirty-eight patients, 18 females and 20 males, with an age range 17–77 years were treated. Most of the patients were in the 5th, 6th, and 7th decades. One had an esophageal fistula, six had gastroduodenal, seven jejunal, 19 ileal, and five had the fistula in the colorectal portion of the gastrointestinal tract. In two cases of ileocutaneous fistula and in one case of colocutaneous fistula, internal fistulae were associated. Most of the patients were extremely ill. Twelve of the 38 patients originally came from other hospitals with established fistulae and in three instances after secondary surgical procedures had failed to correct them. Inflammatory bowel disease was the main original cause (Table 1) of spontaneous external fistulae of the gastrointestinal tract. Surgical procedures attempted for the treatment of such inflammatory bowel disease were the chief etiological factors of postoperative fistulae. Thus surgical complications or anastomotic breakdown were causative in 77% of the fistulae (Table 2).

TABLE 1. *Fistulae and Primary Disease*

Fistula Location	Number of Patients	Primary Disease
Esophageal	1	Surgical injury-vagotomy for ulcer
Gastric	1	Abdominal contusion
	1	Gastric ulcer
	1	Postop chronic fistula
Duodenal	1	Duodenal ulcer
	1	Cholecystitis
	1	Choledocolithiasis
Jejunal	1	Pancreatitis
	1	Pancreatic cancer
	1	Granulomatous colitis
	1	Ulcerative colitis
	1	Diverticulitis
	1	Septic chronic peritonitis
	1	Ulcer disease
Ileal	1	Familiar congenital polyposis
	2	Bowel obstruction
	3	Colonic cancer
	5	Regional enteritis
	3	Ulcerative colitis
	1	Granulomatous colitis
	3	Diverticulitis
	1	Cancer of the bladder
Colonic and Rectal	1	Regional enteritis
	1	Ulcerative colitis
	2	Cancer of rectum
	1	Peritonitis
Total	38	

Fistula Drainage

The amounts of fistula secretion were variable, with drainages ranging 50–4000 cc daily, but predominantly high in most cases. The average output was 800 cc for one esophageal fistula, 600 cc/day for gastroduodenal fistulae, 904 cc for jejunal, 763 cc for ileal, and 387 cc for colorectal fistulae. The high drainage in most cases led not only to malnutrition (a common accompaniment of such fistulae) but to serious electrolyte imbalance.

Treatment Program

As soon as the fistula was recognized or the patient received in transfer from another hospital, a subclavian line was placed and oral intake omitted. Total parenteral nutrition was carried out by a subclavian or internal jugular catheter according to a protocol previously described.[4] In addition, all patients received blood and albumin infusions as well as electrolytes, skin care and sump drainage of fistulae.

The mean duration of lack of oral intake in these patients was approximately 40 days with 21 days in the esophageal fistula, 27.5 days in the gastroduodenal group, 39.8 in the jejunal group, 47.5 in the ileal group and 37.4 in the colorectal fistulae. The average duration of parenteral nutrition was 21 days for the patient with esophageal fistula, 36.5 days for gastroduodenal fistulae, 86.6 for jejunal, 69.12 for ileal, and 50 days for colorectal fistulae. A variety of solutions was used and the total duration of time for which all the patients received hyperalimentation was 2311 days. Solutions used were protein hydrolysate in 32 cases, a synthetic amino acid

TABLE 2. *Fistulae and Etiological Factor*

	Esophageal	Gastric	Duodenal	Jejunal	Ileal	Colonic/Rectal
Surgical Complication						
Anastomosic breakdown		3	2	2	3	2
Injury	1			4	11	1
Persistent Gastrostomy Drain		1				
Inflammatory Disease				1	3	1
Undetermined					2	1
Total	1	4	2	7	19	5

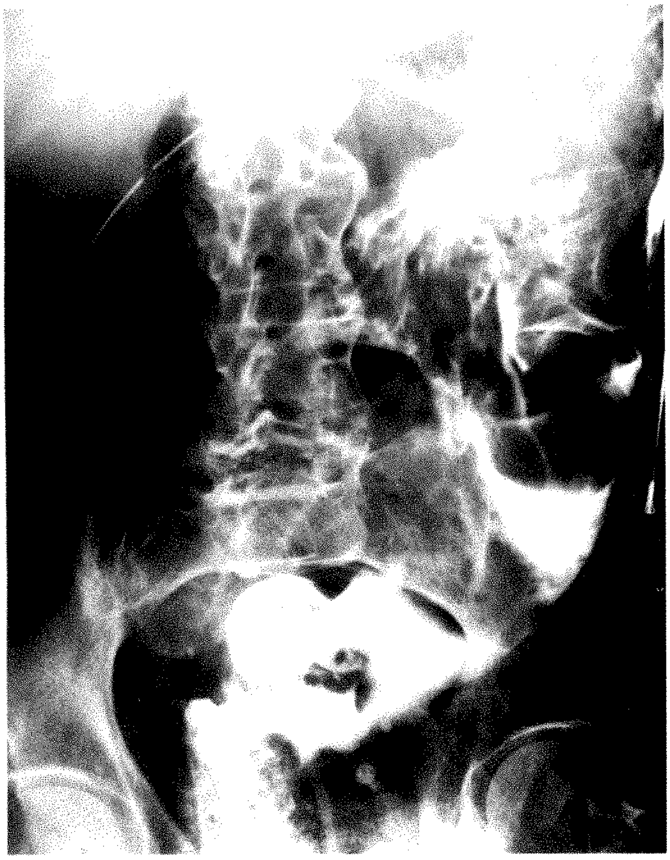

FIG. 1. Extensive intra-abdominal abscesses, an example of which is given, are often related to lack of spontaneous closure of fistulae with hyperalimentation. In this case the sinogram demonstrates an extensive abscess following total colectomy for granulomatous colitis, starting in the left upper quadrant, communicating with another sinus and fistula in the left lower quadrant and exiting from the perineal wound. Operation was required to close this patient's fistula.

protein source and dextrose in four cases (Freamine®) intralipid®* in another and mixture of essential amino acids and hypertonic dextrose (Freamine E®†) in one patient with impaired renal function. The daily rate of calories given ranged between 2,000 (in a patient with renal failure) and 4,500. Between nine and 20 g of nitrogen were administered in 24 hours. Eighty-five subclavian catheters were used in 38 patients, the average duration per catheter being 27.9 days. Most of the catheters were changed at various intervals because of suspected catheter sepsis, ultimately not confirmed by blood or catheter tip culture.

As soon as the patient was physically able to tolerate an hour session of fluoroscopy, he was fluoroscoped by the radiologist and the responsible surgeon with thin catheters and hypaque inserted into all identifiable orifices. The purpose of such fluoroscopy with both the surgeon and the radiologist present was to identify: 1) the site of the fistulae; 2) whether the bowel was in continuity; 3) whether there was any distal obstruction; 4) the nature of the bowel immediately adjacent to the fistula; and 5) the presence or absence of an intra-abdominal abscess either in conjunction with or immediate adjacent to or remote from the site of the gastrointestinal cutaneous fistula. At this time it was at least possible to get a preliminary idea of the anatomical arrangement. Extensive intra-abdominal abscesses (Fig. 1) or lack of continuity of bowel (Fig. 2) (i.e., the fistulagram failed to visualize both ends of the bowel) proved to be the most significant factors in preventing spontaneous closure. Under the circumstances, attempts to obtain spontaneuos closure of fistulae with prolonged hyperalimentation failed. It soon became clear that a certain number of fistulae would not close spontaneously. In the later stages of the study, the responsible surgeon often could identify these cases from the initial fistulagram.

Results

Spontaneous Closure

Only 11 of the 38 patients closed their fistulae spontaneously. One esophageal fistula closed in 17 days. One had a gastric fistula which closed in 61 days, two had duodenal fistulae which closed in ten and 15 days, three had jejunal fistulae which closed in 15, 16, and 40 days

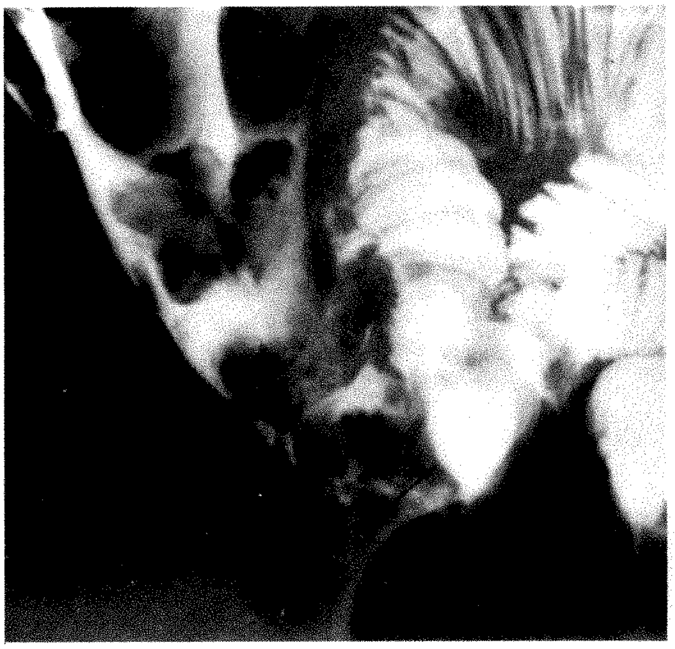

FIG. 2. Lack of continuity of bowel as demonstrated on an upper GI Series. In this patient an end fistula caused by disruption of an anastomosis is seen. Bowel empties directly into an abscess cavity of rather large proportions and empties through a fistulous communication with the skin. Operation was, of course, required to close this fistula.

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* Courtesy Dr. Manuel Tascon, Cutter Laboratories.

† Courtesy McGaw Laboratories, Glendale, California.

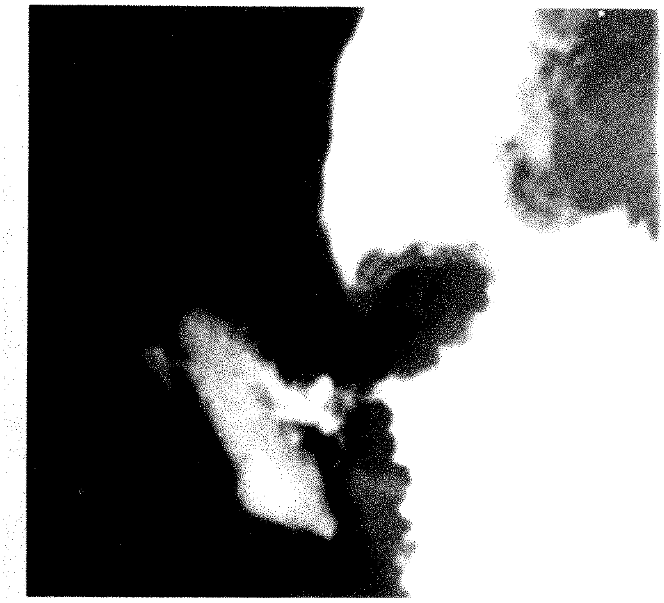

FIG. 3. An example of a fistula which can be expected to close spontaneously with hyperalimentation. The fistula is lateral and probably related to the end of a gastrojejunal anastomosis. Note that although there is an abscess in contiguity with the fistula, the abscess cavity is small. The fistula is lateral through the bowel and the bowel wall appears relatively normal, uninflamed and intact except for a small fistula. This fistula closed with 16 days of hyperalimentation.

and four had ileal fistulae which closed in 18, 21, 41 and 49 days (Fig. 4). The remainder of the patients required surgical intervention as a result of fistula complications, namely intraperitoneal abscesses, distal obstruction or persistent drainage. The indications for operation are summarized on Table 3. Persistent fistula drainage and intraperitoneal abscesses were by far the most important indications for surgical therapy. The operations performed for fistula treatment are varied and are given in Table 4. The most common operations were direct attacks on the fistula with bowel resection plus primary anastomosis either with or without abscess drainage.

TABLE 3. *External Gastrointestinal Fistula Indication for Surgical Treatment*

	Gastroduodenal	Small Bowel	Large Bowel
Persistent fistula drainage		8	2
Intraperitoneal abscess	2	8	3
Intraperitoneal abscess plus obstruction		1	
Obstruction		1	
Bleeding	1		
Peritonitis		1	
Total	3	19	5

Metabolic Parameters

After hyperalimentation, most patients, even those requiring operation, showed a remarkable improvement in their appearance, with weight gain, apparently positive nitrogen balance and general increase in their feeling of well-being. Proteinemia improved in 24 patients, did not change significantly in 12, and diminished in two; this in spite of massive albumin infusions (as much as 200 g daily). The albumin/globulin ratio increased in 15, and remained unchanged in the others. In 31.5% of the patients comprising three gastroduodenal, one jejunal, seven ileal and one colorectal fistula, the amount of daily secretion decreased significantly after hyperalimentation was started. In the remainder of the cases, changes were insignificant. Fourteen patients gained an average of 10.18 lb during the entire course of hospitalization, including surgery. An additional ten lost 10.7 lb

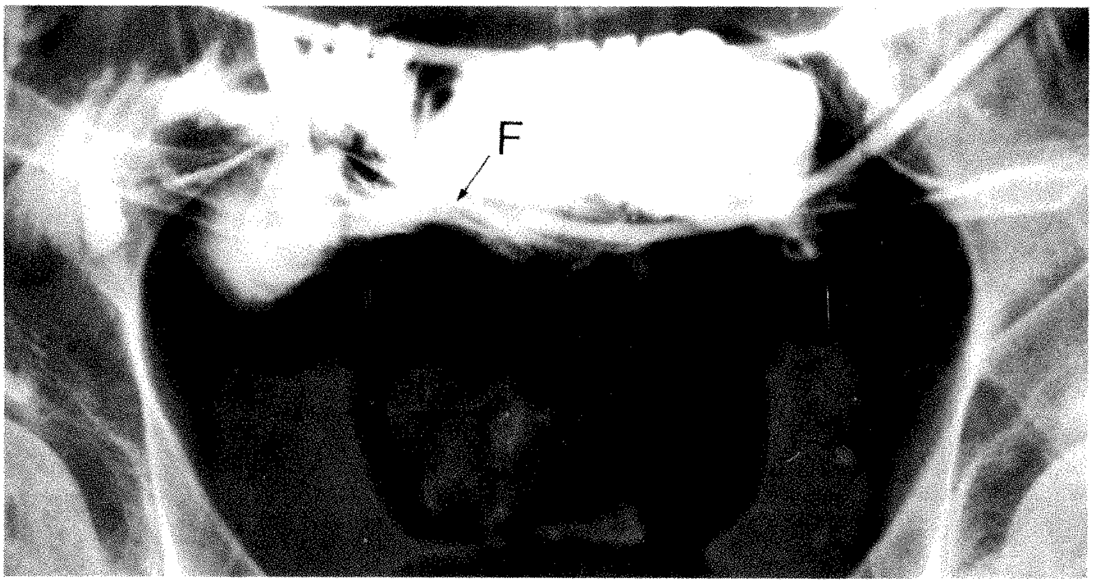

FIG. 4. Another example of a fistula which may be expected to close. Sinogram of an ileal fistula secondary to operative trauma. The bowel wall is intact and, again, is relatively uninflamed. The fistula is small as compared with the bowel circumference and appears to be entirely lateral. This fistula closed after 41 days of hyperalimentation.

TABLE 4. *Operations for Fistula Treatment*

Type of Procedure	Fistula Location Gastric	Small Bowel	Large Bowel
1. Exploratory laparotomy	1		
2. Bowel resection plus			
External diversion		3	
Fistula closure		2	
Primary anastomosis		4	2
Primary anastomosis and abscess drainage		5	
Bypass procedure		1	1
3. Bypass procedures			
Partial		1	
Partial plus external diversion		1	
Total plus external diversion		1	
Total plus abscess drainage		1	
4. Fistula closure		2	
Plus abscess drainage	1	1	
5. Abscess drainage		1	2
Plus external diversion	1	1	1
Total	3	24	6

TABLE 5. *Fistula Complications*

Complication	Gastroduodenal	Small Bowel	Large Bowel
Bled from fistula	2	2	
Anemia	1	6	
Malnutrition	3	15	3
Pulmonary complications			
Pneumonia	3	2	1
Pulmonary embolus			1
Infection			
Wound infection	3	15	2
Intraperitoneal abscess	1	9	3
Peritonitis		1	1
Sepsis	1	7	2
Electrolyte Imbalance	2	4	1
Obstruction		1	
Wound dehiscence	1	2	
Renal failure			1
Jaundice			1
Skin digestion		6	1
Depressive state		6	

during their hospitalization; in the majority of those who lost weight, rampant sepsis ultimately leading to death was responsible for the weight loss. In others, massive anasarca was present when patients were admitted. A period of initial hyperalimentation was followed by massive diuresis so that with the fluid shifts in this group of patients weights were unreliable. A few patients, including those with uncontrollable sepsis, intraperitoneal abscesses or generalized peritonitis, did not gain weight despite the 5 or 6,000 cal infused daily and with an adequate level of insulin to prevent hyperglycemia. In an additional 13 patients, accurate weight measurements were not possible even when bed scales were used and these patients are not included in these calculations.

Certainly the metabolic advantages of hyperalimentation are quite apparent from this study. Hypoproteinemia was corrected in most of the patients but remained resistant in spite of massive albumin infusions in 14 of them. In contrast to the other reports[6] the initiation of total parenteral nutrition and bowel rest did not result in decreased fistula drainage in approximately two-thirds of the patients. We were at a loss to explain this disparity in results, but presumably it reflects the greater incidence of surgical complications in this group of patients in which anastomotic disruption or end bowel fistulae draining into an abscess cavity were present.

Operative Results

In only two (one jejunal and one ileal fistula) of the operated patients who survived, the fistulae did not heal before hospital discharge. In both, a little drainage persisted for long periods after partial bypass in one and total bypass in the other, but eventually closed. Bypass procedures have been reported as less effective than resection or external diversion in the surgical treatment of gastrointestinal fistulae.[3,7,18] Thus, the overall operative success rate is 70.48% in the total number of patients. Five patients (one jejunal, three ileal, and one colonic fistula) had more than one operation for the treatment of complicated fistulae and two of them died with uncontrollable septic complications and re-fistulization. The other four deaths in the group were also patients who had intraperitoneal abscesses and who required operation, with bowel resection or bypass procedures performed in addition to drainage of abscesses; these anastomoses were done in a septic field. It should be emphasized that the principal indication for surgical procedures in the present series was intraperitoneal infection, related closely to the high incidence of inflammatory bowel disease among the primary diseases that predispose to fistula formation. Other factors could be the great proportion of patients referred with complicated fistulae after failure of medical or surgical therapy.

Complications of Parenteral Nutrition

Parenteral nutrition was not exempt of complications even though there were no serious consequences in this

TABLE 6. *Complications of Parenteral Nutrition*

Positive Catheter Culture	5
Clinical Catheter Sepsis	2
Elevation of SGOT LDH and ALK PHOS	2
Hypercalcemia (? Vit D Intox)	1
Hyperglycemia	1
Overhydration	1
Hematoma neck	1
Phlebitis SC vein	1
Subcutaneous emphysema	1

group of patients. In one patient, yeast septicemia was confirmed by catheter tip and blood cultures; the clinical picture subsided after the catheter removal and the patient has remained free of yeast sepsis over the past year of followup. In four other cases *staphlococcus epidermidis* or *staphlococcus aureus* was found in the catheter tip culture although this was not associated with a picture of catheter sepsis as defined in this institution[9] nor did the septic focus appear to subside after catheter removal. A high incidence of positive catheter cultures in spite of the absence of clinical catheter sepsis has been noted by other observers.[9] Other complications, metabolic or related to catheter insertion technique are listed in Table 6.

Deaths

Eight patients in this series died. One had a gastric fistula, which bled massively and two had jejunal fistulae complicated with multiple intra-abdominal abscesses, sepsis and malnutrition. Three had ileal fistulae with sepsis, multiple abscesses being the cause of death in two and bowel obstruction shortly after fistula closure the fatal complication in the third. Two other patients died of large bowel fistulae complicated by widespread intraperitoneal and extraperitoneal sepsis plus renal failure in one and fatal pulmonary embolism in the other.

Among the rest of the patients complications due to the fistulae were mainly infectious. Others, shown in Table 5 include electrolyte imbalance malnutrition, anemia, wound dehiscence, skin digestion and especially a common mental or depressive syndrome in these patients, some of whom had long months of hospitalization.

Discussion

Surgical complications following operations for complicated digestive disease continue to be the principal etiological factor in external gastrointestinal fistula formation.[3,7,8,10] In our group of patients, as shown in Table 2, surgical injury in 17 cases and anastomostic breakdown in 12 caused 29 (77%) of the 38 fistulae. Inflammatory bowel disease, cancer and miscellaneous pathological conditions were the primary course in the rest of the patients.

The first goal in the treatment of these acutely-ill patients is the restoration of blood volume and the achievement of an accurate fluid and electrolyte balance. Blood transfusions and infusions of volumes of albumin are currently used as well as infusion of electrolyte solutions. Skin care is also a chief concern and wound inspection and drainage of any superficial abscess is performed when necessary. A subclavian catheter is placed immediately and total parenteral nutrition started, with the objective of an intake of 4000–5000 cal/24 hours.

The most thorough evaluation of the gastrointestinal tract is desirable in order to establish the nature and location of the fistulous lesions. Sinograms with fluoroscopy are done as soon as the condition of the patient and the anatomical condition of the fistula make is possible. Of great importance is the collaboration of surgeon and radiologist when sinograms are performed, since their interpretation is often difficult. Dye injections, generally 60% Renografin® or Hypaque® in every single fistula opening are helpful in determining the characteristics of fistulous tracts and their connections with bowel loops. Barium or gastrografin exams, carefully done, are also helpful, either performed orally or per enema. If large abscess, distal obstruction or intestinal discontinuity are present, surgery should be done as soon as the patient's general condition makes it safe. Weight gain and improved appearance usually require a period of three to four weeks. In our series intraperitoneal abscesses were present in 14 cases and peritonitis in one. Distal obstruction obliged surgical treatment in only one instance (Fig. 5).

Persistent fistula drainage is another indication for operative management of fistulae. Although parenteral nutrition has obviated the need for surgical procedure to control massive fistula losses, ten of our patients re-

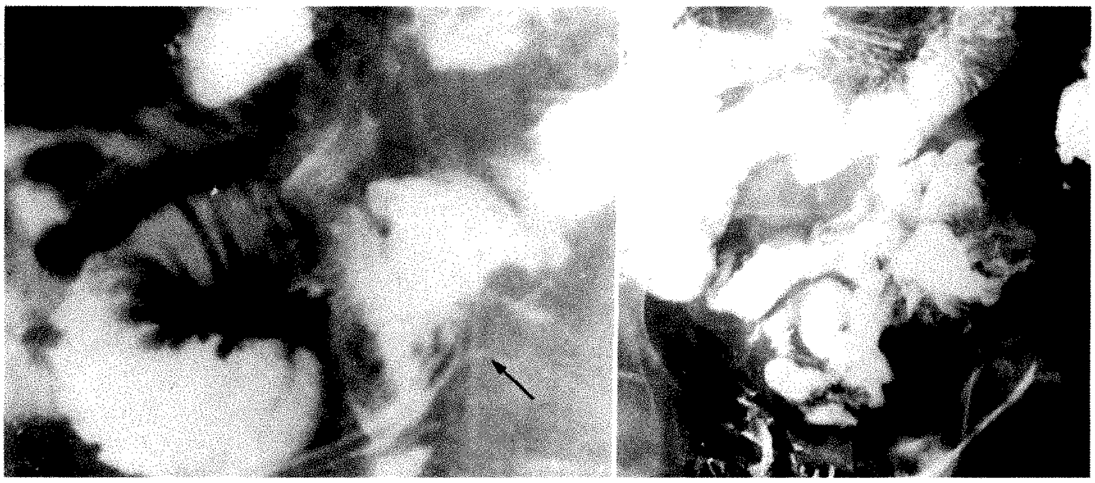

FIG. 5. A composite of x-rays in a fistula, which although lateral, did not close because of distal obstruction. Patient underwent multiple operations because of inflammatory bowel disease. Note that there is a great deal of inflammation of the surrounding small bowel. All of the bowel remains in continuity, distal obstruction necessitated operative correction.

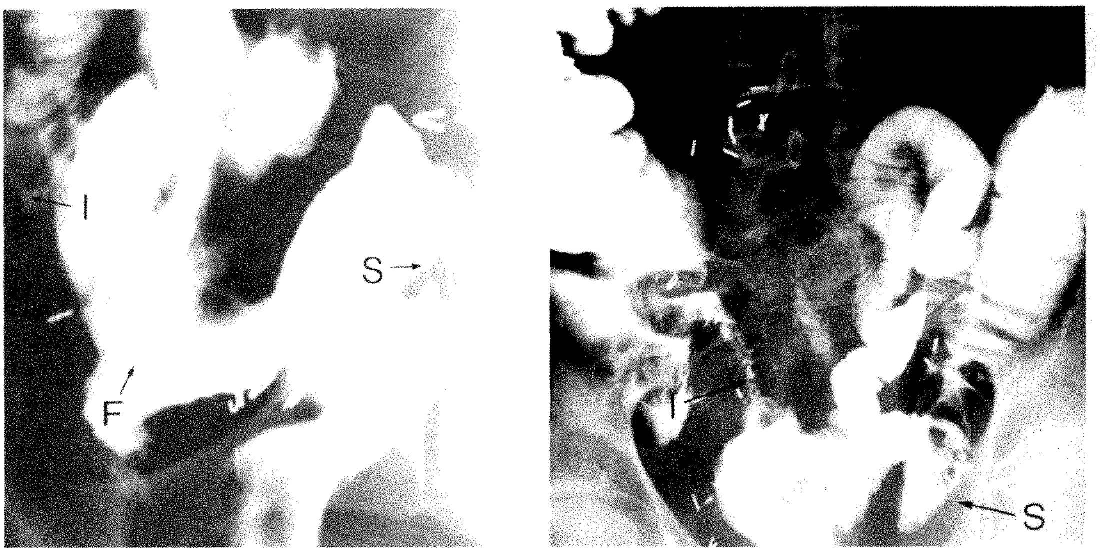

FIG. 6. A spontaneous ileo-sigmoid cutaneous fistula in a patient who had undergone radical cystectomy and ileal loop as well as super voltage radiation one year earlier. This patient also had a small bowel fistula at the time of his previous surgery which had closed with hyperalimentation. Presentation was after cramps suggesting intestinal obstruction and the fistula presented through a lower abdominal wound. This closed after approximately 25 days of parenteral nutrition as well as an elemental diet yielding up to 6,000 cal/day. Inflammation remains around the rectum and the patient has intermittent low grade obstructive symptoms and may ultimately require diverting colostomy.

quired operation for persistent fistula drainage in spite of prolonged hyperalimentation, bowel rest and no abscess or distal obstruction (Table 3).

Following the above outlined program 11, or 30% (one esophageal, three gastric, three jejunal and four ileal fistulae) (Figs. 3, 4, 6, 7) spontaneously closed their fistulae. However, most of the rest of the patients who required operation showed remarkable clinical recovery before surgery was undertaken. It should be noted that pancreatic fistulae are not included in this series, but in our experience almost always close.

In 1960 Edmunds and associates reported that 78% of the overall deaths in 157 patients with external gastrointestinal fistulae were attributable to electrolyte and fluid imbalance, 61% to malnutrition and 67% to generalized peritonitis. In this series fluid and electrolyte imbalance was not a direct cause of death and malnutrition had a secondary role as a contributory factor in only those patients submitted to two or three successive operations. Infection, however, was the main cause of death.

The importance of the nutritional status in the prognosis of patients with gastrointestinal fistulae has been well documented in previous reports by Chapman and associates, Sheldon and coworkers and recently by McPhayden and Dudrick and by Voitk *et al.*[6,10,11] Hyperalimentation and bowel rest improve significantly the life expectancy in patients with external fistulae arising from the gastrointestinal tract although septic complications are still a serious threat. Our 21% overall mortality represents a significant improvement over the previous figures reported from this institution.[3,12,13] The few com-

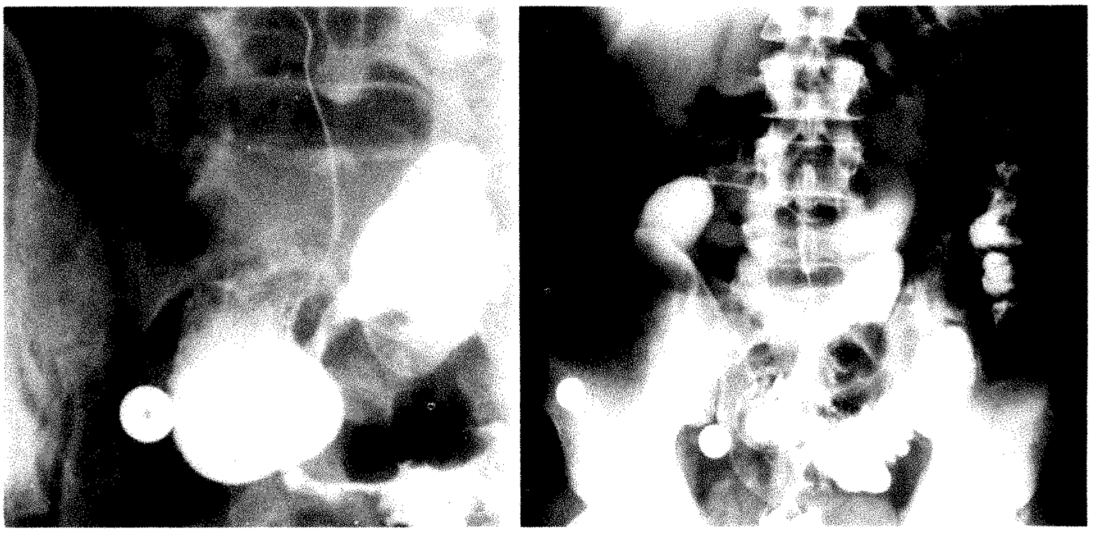

FIG. 7. An internal fistula associated with a ceacal-cutaneous fistula in a patient with Crohn's Disease. The fistula is seen to communicate between the cecum and the rectum. This fistula closed spontaneously with hyperalimentation only to reopen several times and resection was undertaken primarily at the patient's request. At the time of operation two fistulae to the rectum were found which were closed. Diverting colostomy was not used but a gastrostomy was placed and the patient kept NPO and on parenteral nutrition for two weeks following operation. A benign postoperative course resulted and the patient has been well since.

TABLE 7. *Surgical and Conservative Treatment of External Gastrointestinal Fistulae*

Author and Year	Number of Cases	Fistula Location (External fistulas)	Medical Management (% of cases)	Surgical Treatment (% of cases)	Overall Mortality
Edmunds, H., Williams, G. M., Welch, C. E. 1960	157	Gastroduodenal, small bowel, large bowel	22%	78%	44%
Lorenzo, G. A., Beal, J. M. 1969	18	Small bowel	8.6%	91.4%	30%
Nassos, T. P., Braasch, J. W. 1971	21	Duodenal, small bowel	33.4%	66.6%	22%
Sheldon, G. F., Gardiner, B. N. Way, L. W., Dunphy, J. E., 1971*	51	Gastroduodenal, small bowel, large bowel	36.3%	64.7%	12%
Roback, S. A., Nicoloff, D. M. 1972	55	Small bowel	40%	60%	30%
McPhayden, B. V., Dudrick, S. J. 1973*	61	Gastroduodenal, small bowel, large bowel	81.9%	18.3%	6.5%
This paper 1974*	38	Gastroduodenal, small bowel, large bowel	29.0%	71.1%	21%

* Parenteral nutrition was used.

plications related to intravenous nutrition in our patients did not have great importance in the clinical course but have to be considered in view of their potential significance.

While we would agree with all who have emphasized the nutritional needs of patients with gastrointestinal fistulae, the disparity between our results and the results reported by McPhayden and Dudrick remain to be explained, although they seem to be related with a different patient population. In fact, only 54.6% of the upper gastrointestinal and 38% of the large bowel fistulae in these author's series were related to surgical injury which, in this series, constituted etiology in 77% of the patients. It is well known that surgical complications lead often to complete or almost complete bowel disruption and to intraperitoneal abscess formation, precluding spontaneous fistula closure.

The proportion of surgical and conservative treatment of external gastrointestinal fistulae in recent series is shown in Table 7, and the figures of those who have incorporated parenteral nutrition or elemental diet to the general plan of treatment still indicate the necessity of surgical procedures in a great number of patients.

Parenteral nutrition has revolutionized the treatment of external gastrointestinal fistulae since it is no longer imperative that early operation be carried out to avoid irreparable metabolic and nutritional derangements and because it is now possible to get positive nitrogen balance, weight gain and wound healing in patients with a crippled gastrointestinal tract. The role of hyperalimentation, however, and the benefits of an extended conservative management should be estimated as limited in the presence of anatomical conditions, intraperitoneal sepsis, distal obstruction or persistent drainage after the recovery of the nutritional status. The establishment of these criteria will improve, in our opinion, the comprehensive management of gastrointestinal fistulae.

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DISCUSSION

DR. HENRY T. RANDALL (Providence, Rhode Island): Dr. Welch, Dr. Dunphy, and other members of this Association have pointed out the high mortality of high-output gastrointestinal-cutaneous fistulas, as seen over the period ending about five years ago. At that time methods of nutrition were substantially improved, thanks to the contributions of Dr. Dudrick, Dr. Rhoads, and their associates. The striking mortality reduction with adequate nutrition is well pointed out by Dr. Fischer, with a death rate of only eight of 38 of his patients. We have had a similar experience which I would like to relate.

(Slide) This is a series of 37 cases, one less than reported by Dr. Fischer and colleagues. These represent a distribution of high fistulae, 12 cases in stomach and duodenum; 16 mid-gut cases in the small bowel, and 9 low, colonic fistulae. Operative closure in our series is now seven patients; six when we reported this, and one later surgical repair. We have a much higher percentage of spontaneous closure, 65% over all, including a patient with a chronic fistula which eventually healed after several months.

(Slide) After seeing Dr. Fischer's abstract, we further broke down—Dr. Rocchio and I—our results. In the spontaneous closure group of 24 patients, the mean period to closure from the beginning of treatment was 33 days, somewhat less than Dr. Fischer's more prolonged period of about two months. In those in the group which we elected to close surgically, it was about 64 days before we made that decision.

I must emphasize the importance of calories, as he did. We were not able to achieve quite as high a caloric intake, but did average 2600–2800 cal/day, using a combination of high caloric intravenous nutrition and elemental diets. Our series were all treated with elemental diets at one point or another in their course.

Twenty nine, or 78% of our series of patients, had postoperative fistulae, so the two series are very similar. Intraabdominal infection was present in 23 of 31 survivors. We had six deaths, four due to carcinomatosis, one to a g.i. hemorrhage, and one to a pulmonary embolus.

Of 24 postoperative surgical fistula cases that survived, we had only three patients we had to close surgically. There were two additional cases in which diversionary procedures—one ileostomy and one transverse colostomy—were done, and there were 19 spontaneous closures, or 79% of postoperative fistulae.

The two series are both small, but I think there is even a higher percentage of probability of spontaneous closure than Dr. Fischer's series showed. The difference may well be due to the difference in types of patients; we had far fewer cases with end bowel fistulas.

DR. STANLEY JOHN DUDRICK (Houston): I think, in support of Dr. Randall, that differences in data are related primarily to differences in types of patients treated. From the beginning we did not attempt to close the fistula that resembles an ostomy; nor did we try to achieve spontaneous closure of totally disrupted bowel anastomoses.

If one has a superficial fistula, like some presented here by Dr. Fischer, it will not close, in our experience. Thus we don't waste a lot of time trying to close it spontaneously; but we do try to get the patient into good enough nutritional shape that we think we can operate on him under safer conditions than he would have been operated upon had we not replenished his nitrogen stores and improved his strength and caloric reserve.

(Slide) These are the data that we had collected in the original hyperalimentation-fistula series, and we have increased the series now to over 100. We were unable to close only 17 fistulas in this series, but did close them surgically after a brief period of total parenteral nutrition and bowel rest. Six never did close, and one didn't remain closed even after reoperation.

(Slide) These are the types of primary diseases, and the amount of time it takes to close enterocutaneous fistulas with these different diseases. With inflammatory bowel diseases, the fistulas close earlier, but these are generally narrow fistulas with long tracts in contrast to total to total disruption of the anastomosis or a total wound disruption in which an ostomy type opening, which won't close, might be present.

(Slide) Of the 62 patients in this series, four, or 6.5%, died.

(Slide) These are some data from the literature. Dr. Fischer has already referred to the Mass. General series. Notice that what goes through this progressive line of decreasing mortality is that in each one of these series, an increasing amount of attention is paid to the nutritional status of the patient. And as one evaluates the local wound care of the patient, the operative expertise involved, and the types of patients treated, they were equal; and the reduction in mortality in these series is related directly to the increased attention given to nutrition.

(Slide) These are the principles that we reported a few years ago and the priorities for management of fistulas. We try to get radiographic identification of the type and location of the fistula as soon as possible, and, hopefully, within the first week. Dr. Fischer did emphasize a very good point: the identification of these fistulas should be done with the surgeon and the radiologist in attendance, to reduce the risk of the procedure in a patient who is already rather cachetic and weak, and to insure that the data obtained are clearly defined and meaningful.

If the fistula doesn't close within about four weeks, or 30 days, the chances are that it's not going to close. However, we don't feel this penalizes the patient, because subsequent operation on patients who are in better metabolic and nutritional status will yield a lower mortality, a lower morbidity, and an eventual higher salvage rate in these critically ill, complicated patients.

DR. CLARENCE DENNIS (Bethesda): In view of the report several years ago by Dr. Max Gaspar that the incidence of fistula after anastomoses is cut in half if a closed anastomosis is done instead of an open one, I wonder if Dr. Fischer was able to find data on patients who come in with postoperative fistulas regarding how the anastomoses were done in the first place.

DR. JEROME J. DECOSSE (Milwaukee): In our enthusiasm for the obvious benefits of parenteral hyperalimentation, we have asked ourselves about its role in the context of other existing therapy. Specifically I'm concerned about the value of a feeding jejunostomy in control of a high gastrointestinal fistula. That has not been alluded to in Dr. Fischer's address. I wonder if Dr. Fischer might respond by indicating the relative role of a well-constructed feeding jejunostomy in such patients.

DR. JOSEF E. FISCHER (Closing discussion): Both hyperalimentation, done according to the Dudrick technique, and elemental diets, we feel, have a role in the treatment of these patients, and we use both. We use them not interchangeably, but often in combination, since one can get up to very high caloric intakes—about 6000 cal—which we feel might heal a little faster than just hyperalimentation alone.

I think the answer to the differences between the series lies, as all the discussants have said, in the patient selection, and in various series the postsurgical fistulae have ranged from 80%, or 77% in our series, Dr. Randall's series, to much lower figures, and, depending on what patients you get, basically there will be a certain outcome.

In answer to Dr. Dennis' question, we do have the data. There were very few if any closed anastomoses done in this group of patients, whether done in our own hospital or when we saw the operative notes of patients received in transfer from other institutions.

I think Dr. DeCosse brings up a very good point, and one which we did not have the opportunity to cover in the presentation. (Slide) The question of proximal decompression jejunostomy, gastrostomy, indwelling tubes, I think, is a very real one. Prolonged Levin tube intubation in six of the patients has resulted in typical strictures here. (Indicating) This is possibly the worst one. This patient has four feet of bowel and swallows dilators every day. I have been reluctant to take him on with a long stricture; but the presence of an indwelling tube, instead of a Levin tube, in this group of patients might obviate the presence of strictures, both in the decompression, and certainly for feeding of either elemental or tube feedings in this group of patients.

Chronic Tissue Insulin Resistance Following Hemorrhagic Shock

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Metabolism of fat and muscle tissue was measured for 30 days following shock and reinfusion in rabbits. Tissue insulin resistance in the post-shock period was demonstrated by decreased oxidation of glucose and decreased incorporation of glucose into neutral lipid or glycogen during incubation with insulin. In addition, the insulin stimulated incorporation of amino acids into muscle protein was markedly reduced after shock. Conversely, the capacity of muscle to oxidize leucine was enhanced by shock, even in the presence of insulin. Tissue insulin resistance and increased leucine catabolism are likely to contribute to the general metabolic response to shock and trauma.

MAJOR TRAUMA or shock are commonly associated with glucose intolerance[15,18,21,33] resistance to administered insulin,[18,23] and excessive urinary nitrogen loss[10,11] which is not reversed by provision of carbohydrate.[6] These abnormalities usually persist for several days after injury, even though often accompanied by elevated circulating insulin levels.[7,19,25] This report describes an investigation of tissue glucose and amino acid metabolism as influenced by insulin following hemorrhagic shock with reinfusion. The data show a defect in tissue insulin sensitivity, with corresponding impairment of insulin regulated metabolism, which persists for at least one week after re-establishment of normal blood volume and pressure.

Methods

Albino rabbits (3–5 kg) of either sex were subjected to hemorrhagic shock while anesthetized with 0.2 mg pentanyl plus 10 mg droperidol (Innovar-Vet, Pitman-Moore) per kg. A mean blood pressure of 30 mm Hg was established by withdrawal of venous blood into a heparin containing reservoir. This pressure was maintained for 30 minutes by adjusting the volume of blood withdrawn. At the end of the shock period 80% of the shed blood was reinfused at a rate of 2 ml/min. Control animals were anesthetized but not cannulated or bled. The three-day survival of the shock group was 43 of 47 animals, excluding those which died during or immediately following the hypovolemic period (8 animals). Samples of skeletal muscle and adipose tissue were obtained sequentially for one month following shock. The animals were anesthetized, samples of the transversus abdominus muscle were prepared by excising narrow bands (0.75 cm by 3 cm) separated from fascia and surrounding muscle by blunt dissection, and rapidly immersing them into oxygenated buffer containing glucose (18.5 mM). After 5-10 minutes of preliminary soaking to loosen the connective tissue,[29] the muscle was teased into fine strands along the fiber axes. The strands (0.5 mm diameter) were not completely separated from one another and the result was a group of "puffs" of muscle tissue. Preparation in this manner allows the cut ends to coagulate,[29] providing a central region of metabolizing muscle able to contract when stimulated electrically,[29] with intact energy generating processes,[14,17] normal membrane permeability,[29] and normal striations and transparency,[17,29] but with adequate surface area to allow proper diffusion of metabolites. This technique provided skeletal muscle which would respond to insulin

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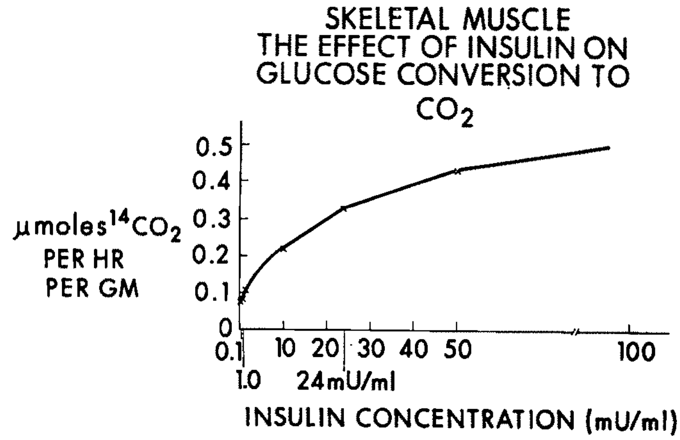

FIG. 1. Dose response for the effect of insulin on the conversion of glucose to CO_2 by rabbit skeletal muscle. Each point represents the mean of 4–6 determinations except for control (10 determinations) and 0.1 mU insulin (10 determinations). Standard deviations were all less than 5 percent of the mean and are not shown. All points indicated were significantly elevated above control, $p < 0.05$.

(Fig. 1), with a sensitivity similar to that of the intact rat diaphragm preparation.[24] The minimum insulin concentration producing a detectable response in muscle from normally fed rabbits was 0.1 mU/ml. Except as otherwise noted, incubation with insulin refers to 24 mU of regular insulin (Sigma) per ml of incubation medium. All of the effects of hemorrhagic shock described in this report were also apparent when studied with 100 mU of insulin per ml (not shown).

Glucose metabolism was studied using Krebs-Ringer bicarbonate buffer, containing 18.5 mM glucose and 0.50 microcurie glucose-6-^{14}C tracer per ml, equilibrated with O_2-CO_2 (95:5). Tissues were incubated for 90 minutes at 37 C with shaking. At the end of the incubation, phenethylamine HCL was injected through the rubber cap into a disposable centerwell (Kontes) containing one-half of a gelatin capsule and a glass fiber wick. After 2 minutes, the incubation vessels were briefly uncapped, the tissue removed, the caps replaced, and 0.2 ml of 10 N sulfuric acid was injected into the incubation medium to release the evolved CO_2. Prior experiments demonstrated the loss of radioactive CO_2 resulting from this procedure to be undetectable (less than 1%). Glycogen radioactivity was determined by the method of Staufacher and Renold.[32] Leucine oxidation was determined by the method of Odessey and Goldberg,[22] using 0.1 mM leucine and 5.5 mM glucose, with leucine-1-^{14}C tracer.

Adipose tissue obtained from the parasplenic area was divided into uniform fragments (35–50 mg) and three fragments per flask were incubated for CO_2 collection as described above for muscle glucose metabolism. Adipose tissue total neutral lipid radioactivity was determined by the method of Kitabchi *et al.*[20]

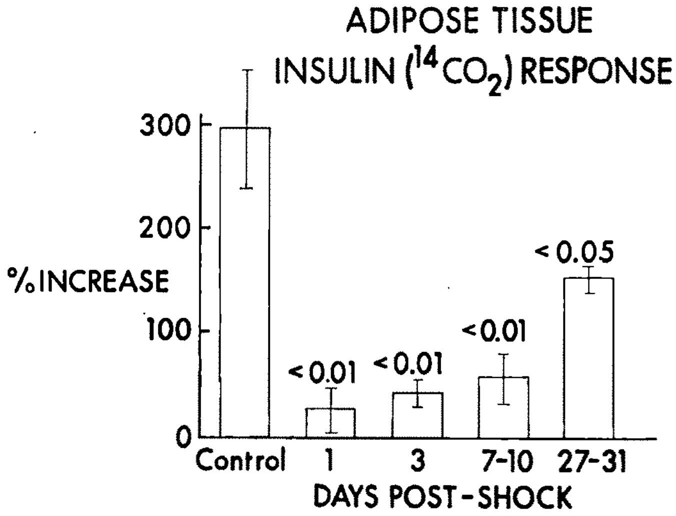

FIG. 2. The per cent stimulation of adipose tissue glucose conversion to CO_2 by insulin (24 mU/ml). Each bar shows the mean ± S.E.M. for 8 or more animals, except 27–30 days (6 animals). Significances indicated are according to the Student's t-test.

Results

The oxidation of glucose to CO_2 by adipose and muscle tissue in the presence of added insulin are shown in Figs. 2 and 3. For at least several post-shock days the tissues were significantly depressed in sensitivity to the effects of insulin, approaching normal sensitivity by one month. The insulin stimulated rate of glucose oxidation by the tissues in the post shock period is shown in Table 1. Insulin stimulated glucose incorporation into adipose tissue total neutral lipids and skeletal muscle glycogen was also impaired following hemorrhagic shock and remained significantly below control levels for at least one week (Fig. 4).

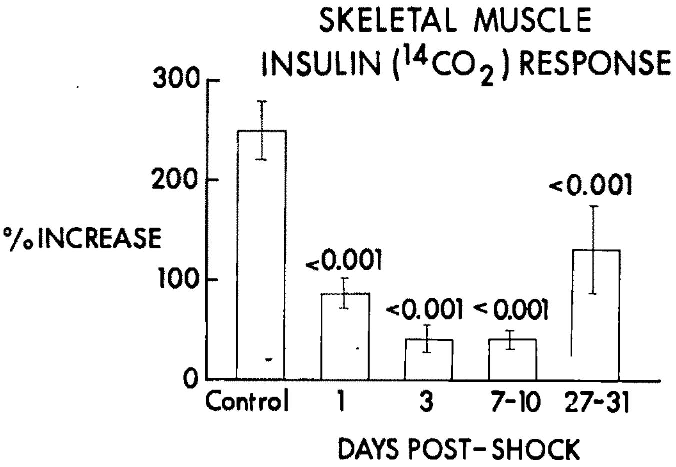

FIG. 3. The stimulation of skeletal muscle glucose conversion to CO_2 by insulin (24 mU/ml). Number of animals and statistical data are as described in Fig. 2.

TABLE 1. *Production of CO_2 in the Presence of Insulin*

	(micromoles per gram per hour)				
Substrate/Tissue	Control	24 Hr Post-shock	72 Hr Post-shock	7–10 Days Post-shock	27–31 Days Post-shock
Glucose-6-^{14}C					
Muscle	0.31 ± 0.04 (12)	0.21 ± 0.01 (10)*	0.20 ± 0.06 (9)*	0.14 ± 0.08 (7)*	0.15 ± 0.05 (6)*
Adipose	0.39 ± 0.02 (12)	0.15 ± 0.02 (9)*	0.25 ± 0.04 (9)*	0.16 ± 0.01 (8)*	0.24 ± 0.02 (6)*
Leucine-1-^{14}C					
Muscle	0.18 ± 0.02 (8)	0.31 ± 0.04 (5)*	0.28 ± 0.03 (8)*		

Mean ± S.D. with the number of observations in parentheses.
* Significantly different from control by Student's t-test, $p < 0.001$.

Amino acid metabolism 1 and 3 days following hemorrhagic shock was studied in isolated skeletal muscle in the presence of insulin. The incorporation of leucine into protein (trichloroacetic acid insoluble fraction), was markedly reduced following shock (Fig. 5) and this alteration persisted for the 3 days of the study. Leucine oxidation to CO_2 was accelerated in muscle tissue obtained 1 and 3 days after shock (Table 1).

Discussion

This report contains the first direct evidence of a persisting alteration in muscle and adipose tissue metabolism resulting from hemorrhagic shock. Previous studies have described changes in tissue metabolism occurring during the acute hypovolemic period of hemorrhagic shock,[9,12,13] perhaps related to tissue anoxia[1,12,13] or to the acute effects of adrenal cortical or medullary secretions.[30,31] However, the tissue anoxia does not persist long after reestablishment of normal blood volume and pressure, and circulating glucocorticoid[30] and catecholamine[31] levels return to normal within 12–24 hours. In contrast, the sub-normal responsiveness of tissue glucose metabolism to insulin described in this study lasted for one week or longer.

Resistance to the hypoglycemic effect of administered insulin[18,23] and impaired glucose tolerance, despite enhanced insulin response,[15,21,23] have been observed following various forms of injury, the magnitude of the abnormalities being related to the severity of the injury.[18,36] The reduced insulin-stimulated glucose metabolism by adipose tissue and skeletal muscle following hemorrhagic shock, reported here, probably contributes to the abnormalities of glucose tolerance associated with injury.

Another component in the metabolic response to injury which may be partially clarified by our observations, is the prolonged negative nitrogen balance.[5,10] Administration of carbohydrate to normal fasting subjects dramatically reduced the loss of body nitrogen in the urine, but carbohydrate administration to injured individuals is relatively ineffective in preventing the nitrogen loss. Cahill[5] has postulated that reduced tissue insulin sensitivity acts as at least one possible contributing factor in the development of the nitrogen catabolism which follows injury. Our findings of a lower rate of insulin-stimulated protein synthesis in skeletal muscle following hemorrhagic shock supports Cahill's suggestion. However, another possible mechanism to explain the net protein breakdown is suggested by the accelerated oxidation of leucine by muscle in the presence of insulin in the post shock period. It is possible that irreversible combustion of this amino acid may lower its concentration in the intra-cellular protein synthetic amino acid pool, thereby impairing protein synthesis,[28] which appears to be influenced by the concentration of leucine.[3,22] If increased glucose oxidation by muscle plays a role in reversing the nitrogen loss of normal fasting individuals, our finding of reduced insulin stimulated glucose oxidation by muscle after shock would provide another possible explanation for the failure of glucose to reverse the negative nitrogen balance after trauma. The presently available data do not establish the relative importance of these mechanisms in post-trauma protein homeostasis.

The mechanisms initiating the metabolic response to hemorrhagic shock are not clearly defined at present. Hemorrhagic shock stimulates catecholamine and glu-

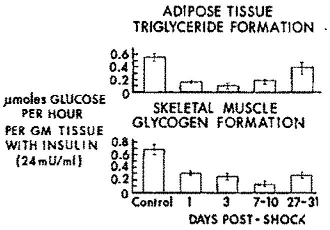

FIG. 4. The rate of conversion of glucose to neutral lipid or glycogen with insulin (24 mU/ml). Number of determinations and statistical data are as described in Fig. 2.

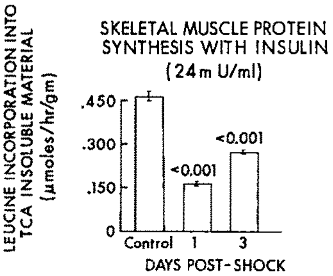

FIG. 5. Leucine incorporation into protein by skeletal muscle in the presence of insulin (24 mU/ml). Each bar shows the mean of 6–8 rabbits. Statistical data are as in Fig. 2.

cocorticoid secretion, as well that of other hormones. Although the levels of the steroids[30] and catecholamines[31] return to normal soon after re-establishment of normal blood volume and pressure, they may contribute in some degree to the observed changes in tissue glucose and amino acid metabolism.[26,27] Epinephrine has been shown in our laboratory to decrease glucose tolerance, even when insulin secretion is normalized by the administration of alpha adrenergic blockers,[16] and in isolated muscle, epinephrine has been shown to decrease amino acid incorporation into protein and to enhance the oxidation of leucine.[2,34] Glucocorticoids are well known for their potent effect of decreasing glucose tolerance,[4] and protein synthesis by skeletal muscle.[35]

Experiments in progress in our laboratory suggest that adrenalectomy, with replacement steroid maintenance, does not completely abolish the effects of hemorrhagic shock on tissue metabolism described in this report. This is in agreement with the results of Chaudry *et al.*[8] which demonstrated reduced insulin stimulated glucose uptake during acute hemorrhagic shock in adrenalectomized rats. Further study is necessary to clarify the factors responsible for hemorrhagic shock-induced alterations in insulin dependent metabolism.

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DISCUSSION

DR. JAMES D. HARDY (Jackson): We too are studying glucose, insulin, and gastrin levels in experimental shock. While not completely analyzed as yet, our data tend to support the work reported by Dr. Egdahl's group in the past. However, I wish to mention a different segment of our shock studies.

After developing models for blood loss shock and for endotoxin shock that were uniformly fatal in the experimental animals we transplanted the hearts from the dogs in irreversible blood loss shock and also from dogs in irreversible endotoxin shock to normal dogs, with virtually uniform survival. (Slide) Similar results were obtained in the monkey. (Slide) This is an oxygen chamber in which the animal receiving the heart transplant is kept for three days. Thus, the heart itself remained capable of normal function if transplanted to a normal animal.

We now plan to employ the "wash-out" technique in the irreversibly shocked dog. The shock animal's blood will be removed with asanguinous perfusate (as published by Neely *et al.* from our laboratory in 1963) and then replaced with fresh blood. The objective is to determine whether, with complete blood replacement, the animal can then be successfully resuscitated. We hope this model will shed further light on the possible presence of a toxin or myocardial depressant factor in irreversible shock.

I would like to ask Dr. Egdahl and his associates whether they determined the biological half-life of insulin in their shock preparations.

DR. GEORGE H. A. CLOWES, JR. (Boston): Shock is a form of tissue injury. Qualitatively exactly the same things happen whether the tissue injury is effected by physical means, by infection, or by lack of perfusion.

(Slide) To illustrate what I mean, and what Dr. Egdahl has shown us—this patient is typical of many who have been in severe shock, and in the post-shock period have high cardiac outputs, far in excess of what would be required for their caloric expenditure. Here is the septic state producing the same thing in this same patient, who had a ruptured abdominal aneurysm, and was in shock for a long period before completion of the operation. Here the caloric expenditure has risen a little bit but again the cardiac output is way out of proportion.

(Slide) Here is a further example of the enzyme data similar to that given by Dr. Egdahl, but in septic animals. Dr. N. T. Ryan, one of the authors of this paper, has measured pyruvate dehydrogenase activity in various tissues of fed, fasted, and septic fasted rats.

Pyruvate dehydrogenase is an enzyme complex which is rate limiting for conversion of pyruvate to acetyl co-A, entering into the Krebs cycle of carbohydrate metabolism. It is very sensitive to insulin. Within 30 minutes it rises on exposure to insulin.

In the fed animal with a high insulin level the activity is high in the diaphragm. In the fasted animal with a low insulin, it's reduced; but in the septic animals that actually have high insulin levels, we see an even further reduction. This is one aspect of insulin resistance in sepsis. This resistance is not present in the liver. The liver behaves differently from muscle liver. Pyruvate dehydrogenase is higher in the fasted septic animal that has a high insulin level.

(Slide) The behavior of adipose tissue in the septic rat when subjected to insulin also is normal. In short, insulin resistance is limited to the muscles in the septic state.

Now, to show how this applies to people, let's look at data taken from a series of patients who were septic. It is not unlike Dr. Egdahl's post-shock situation. The urinary nitrogen excretion in the high flow group was 7.4 g per day, but in the low flow group, who were in a shock state despite a relatively high cardiac output, it was 16 g per day.

Let me pull this together by saying that Dr. Tom O'Donnell has an article in the *Journal of Surgical Research* showing that there is a fuel deficit under these conditions in the extremity of an animal due to the suppression of lipolysis by high insulin levels. This leads to the requirement for the burning of branch chain amino acids to make up for the lack of fat. In the low cardiac output state, insulin is low so that fat is available, but all the glucose is being converted to lactate, again leaving a fuel deficit which can only be met in the muscle by proteolysis.

We would like to propose a hypothesis based on these findings. The fuel deficit in the muscle, or perhaps in peripheral tissues, as shown by Dr. Egdahl and his group, is really a protective mechanism that leads to the mobilization of amino acids to satisfy the muscle's need. Since the muscle can only burn the branch chain amino acids, like the leucine, all the others, such as alanine and glutamine, have to be released and converted to glucose in the liver for further use. We would propose, following the suggestions of Unger and Rocha, that this alanine may be the stimulus for glucagon secretion, which only has its effect in the liver. The net result is that we have an overproduction of glucose, under these conditions to which insulin secretion responds. Perhaps this cycle is a protective mechanism that is a killer if it goes too long.

DR. FRANCIS D. MOORE (Boston) Since the description of a marked draft on body protein in typhoid fever 70 years ago, followed then by the data on fractures in rats and surgical trauma in man, the question has always been: How and why does the body hydrolyze vast amounts of muscle protein, actin, and myosin, and what harm does it do? Is it good or bad, or is it just nature in the raw?

The human being must be hit, and hit hard, to activate this whole mechanism, and it's not found in ordinary clean, elective, mid-grade civilian surgery, as shown by several members of this society; but when the human being is hit hard with a high and lasting catecholamine elevation, insulin inhibition, glucagon activation, and a high pulse of free cortisol, then the draft on muscle protein is truly spectacular, double that in starvation, up to 12–18 g/70 kg/day, and rather insensitive to exogenous substrates.

We have considered catecholamine activation as basic to this chain, and Dr. Pruitt's paper will again return to this topic. Catecholamines inhibit the central production and the peripheral activity of insulin, and markedly stimulate the production of pancreatic glucagon. But this hardly explains the findings of Dr. Egdahl and his coworkers, because they showed us a lasting effect after a very transient injury.

The rabbit eats very little meat; so that the meat diet, high portal vein amino acid activation of glucagon, so prominent in man and in most meateaters, may not be so active, and may be damped. Dr. Unger, both a student and a philosopher of glucagon, has postulated that the pancreatic glucagon, while a nonessential hormone—patients after pancreatectomy get along perfectly well without it—may, in the primitive meateater, prevent hypoglycemic shock after a tremendous meat meal, such as a captured animal.

It could be that we're looking at a special species thing, as a more general phenomenon. The rabbit has few sources of branched chain amino acids, other than muscle hydrolysis.

We would, therefore, like to ask three questions: What is bugging the muscle response to insulin in these rabbits? If it's an energy deficit, why is it so different from starvation? And it is strikingly different.

Secondly, did they ever try giving large amounts of exogenous insulin in the peripheral circulation before the animal tissues were taken, however their experiment was set up?

And lastly—the species difference—have you tried these studies on a meateater?

DR. WILLIAM RICHARD DRUCKER (Charlottesville, Virginia): This work is very closely allied to the work we have been doing over several years. One of the papers that Dr. Moore referred to on the subject of an altered glucose tolerance after injury was a study we did in Cleveland many years ago. We showed that even a relatively minor injury to man, such as an herniorraphy, would produce a transient alteration of glucose tolerance. We extended these studies to show that in patients for whom anesthesia was not necessary in order to perform the surgery—paraplegics—we still found an alteration in glucose tolerance. Even in very severely injured people we found that the glucose tolerance returned to normal within a period of 48–72 hours.

Therefore, I would ask Dr. Egdahl whether he has, or knows in the literature, data indicating that glucose tolerance—which, after all, should reflect any change in insulin sensitivity—whether glucose tolerance remains altered after severe hemorrhagic shock in man.

Looking more specifically at the paper, was the model a proper one? A biochemist looking at this study will ask: How good is this model of an isolated muscle preparation and an isolated fat pad?

I'm reasonably convinced by the fact that he showed similar changes in metabolism in two entirely different types of tissue—muscle and fat—that his model, in effect is excellent, and is demonstrating true changes.

My third question is about the dose response curve. Dr. Moore referred to this when he asked about giving huge doses of insulin prior to taking the muscle and the fat for analysis. I think Dr. Egdahl said that he gave something in the order of 100 units of insulin. Is the dose response curve shifted, or is the V max reduced? This question has tremendous practical application for those of us who treat people in shock. Perhaps by just giving larger doses of insulin, we can break through insulin insensitivity. If, however, V max is reduced, then giving huge doses of insulin will not improve insulin action.

Finally, again speaking from a therapeutic standpoint, and relating to the question that Dr. Moore asked, what is the role of protein in postshock insulin insensitivity? Many years ago Drs. Abbott, Holden, Davis, and Krieger in Cleveland demonstrated that by providing large amounts of protein and calories for postoperative patients, they could reduce or prevent the negative nitrogen balance following injury. In the occasional patient with a postoperative negative nitrogen balance, it rarely exceeded 2–4 g and nitrogen equilibrium was restored within 48–72 hours following surgery.

Is it possible that giving large amounts of protein, or perhaps some specific amino acid mix, will overcome the insulin insensitivity? Perhaps we should direct our efforts to provide a protein meal, rather than give large doses of insulin to the patients who are suffering some kind of ongoing postshock insulin insufficiency.

DR. RICHARD H. EGDAHL (Closing discussion): Dr. Hardy's experiments in heart transplants are very exciting, because for the first time they really show that it's not the heart that's irreversible in irreversible shock. What is the organ or organs that are "irreversible?" We have had many discussions on this subject at meetings of this society.

We didn't measure the half-life of insulin in these animals, but there are studies by Johnson, Stoner, and others that have demonstrated a prolonged half-life for insulin in shock states. However, the half-life returns to normal quickly, far sooner than the animals return to a basal state; so I would suspect the half-life of insulin might be normal in our studies.

George Clowes' discussion was very welcome, and many of the findings of our groups have reinforced each other for the last several years. We find the septic animal a particularly difficult preparation to work with, because so many things are happening—endotoxin release and tissue effects that are very complex—whereas the hemorrhagic shock model, although it elicits all the endocrine responses, resulting in a return of the animal fairly quickly, and that's why we prefer hemorrhagic shock to septic for a stimulus. I simply don't know why abnormal tissue responses last up to 30 days.

I think Dr. Clowes brought up the question about the lack of fuel, and suggested that hypothesis that energy deficits lead to a burning of branched chain amino acids, and this is probably what happens. Perhaps ATP reservoirs are used up. The muscle can't burn other substrates that are not available to it, because of insulin insensitivity, so amino acids like leucine are burned. There is recent exciting evidence by biochemists that the intracellular amino acid branched chain pools are essential for the synthesis of protein, so you can't get proteins being synthesized; some very fundamental mechanism appear to be at work.

Dr. Drucker's question, as well as Dr. Clowes', concern the utilization of amino acids. Dr. George Blackburn's work based upon studies such as we have described today, does show that if one gives amino acids, one can get preferential sparing of protein.

Dr. Moore came through with some very strong and powerful questions for the future. We agree that the rabbit is different, not only as a salad type animal, but because he secretes compound B, largely, rather than compound F, which the carnivores and man do; and we are in the process of studying other animals. The rabbit was a good model for several reasons, because you can get an optimal shock preparation.

We have not administered large amounts of exogenous insulin to this animal preparation, but plan to do so. Pertinent to Dr. Drucker's question, we did find in these *in vitro* preparations that the addition of very large amounts of insulin to the incubate did not change the results we presented. Twenty milliunits, in other words, were the same as 100 milliunits. I do suspect that there are uses for glucose-insulin-potassium in patients, but they are not well defined yet, and certainly should only be carried out in the few centers that are set up to specifically study the results.

We have not studied species differences, but we will.

Dr. Drucker asked the question: Is there any evidence in the literature that glucose tolerance stays abnormal after prolonged periods of shock? There is none. On the other hand, there are bits of evidence here and there that animals which have recovered from a period of shock may have resistance to other forms of shock. What is the cellular basis for this? Is there a change in the ATP levels, or general energy levels in the cell?

We speculate that perhaps what we have here is some intracellular biochemical manifestation, some change that lasts longer than one can identify in the gross biochemical profile of the animal.

Dr. Drucker asked about our model. Dr. Ryan is a Ph.D. biochemist who developed the tissue incubation procedures. I'm satisfied from studying the tissue preparation that standard curves are obtained and that the muscle tissue output in vitro functions the same as the rat diaphragm of Odessey and Goldberg, which is the mark, for that particular biochemical preparation.

We use the rabbit because we need long strands of muscle. They retain their cross-striations in our preparation and have normal membrane permeability. For example, they do not absorb phenol red, and under the EM they look normal. From all measurable standpoints this is effectively functioning tissue for a period of several hours.

We are currently stuck with the question as to why the tissue effects last so long, and all we can say is that there is much work to be done in the next few years to try to unravel the entire sequence of events.

Extravascular Lung Water Following Hemorrhagic Shock in the Baboon:

Comparison Between Resuscitation with Ringer's Lactate and Plasmanate

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Baboons were subjected to deep hemorrhagic shock by using a membrane potential of −65 mv as an endpoint. They were then resuscitated with either Plasmanate plus their shed blood or Ringer's lactate plus their shed blood. As compared with their own preshock values, the Plasmanate-resuscitated animals accumulated more extravascular lung water than the Ringer's lactate-resuscitated animals. Another group of baboons resuscitated from deep shock demonstrated significant extravasation of albumin on postmortem analysis of lung composition. This increased tendency for extravasation of albumin after shock partially explains why resuscitation with Plasmanate gave no protection against the formation of pulmonary edema. The authors believe that Plasmanate, and probably other colloidal solutions, should be used sparingly in the initial treatment of deep hemorrhagic shock.

INTERSTITIAL pulmonary edema is a common consequence of shock resuscitation. The type and amount of fluid used in resuscitation may be important determinants of the amount of edema formed.[2,4,19,21,23,31] The pathophysiological basis for the "wet lungs" may be: 1) decreased serum oncotic pressure;[22,33] 2) increased pulmonary capillary pressure;[7,24,25] 3) increased pulmonary capillary permeability;[1,12,29,30] or 4) a combination of these factors and others.[35]

Resuscitation with colloids, as compared with crystalloids, should help maintain serum oncotic pressure and prevent the net flow of fluid into the pulmonary interstitium. During and after shock, however, capillary permeability may increase, or other forces come into play[18] which would allow extravasation of colloids like albumin. The extravasated albumin would increase interstitial oncotic pressure and neutralize the effect of the intravascular proteins.

These experiments were designed to 1) measure the extravascular lung water accumulated after resuscitation from shock with colloids versus crystalloids and 2) determine if shock itself leads to increased pulmonary extravasation of colloids.

Methods

The experiments were divided into two sets.

In the first set, eight female baboons, weighing 8–15 kg, were tranquilized with Sernylan (1 mg/kg), placed supine on a heating pad, intubated and allowed to breathe spontaneously. A five-French catheter with a gently curved tip and a thermistor attached to the concavity of the tip was inserted through the femoral artery into the abdominal aorta. This thermistor-catheter was used to measure pressures and to obtain thermal-dye extravascular lung waters. A 16-gauge polyethylene catheter was inserted through the axillary vein to obtain central venous pressures. A Swan-Ganz catheter (5 Fr) was inserted through the femoral vein for pulmonary arterial and wedge pressures. Positions of the catheters were confirmed by pressure recordings. Cutdowns and muscle biopsies were done under supplemental pento-

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TABLE 1. *Summary of Hemodynamic Data in Eight Baboons Comparing Resuscitation with RL and PL*

		Study Period						
		Before Shock	Immediately After Resus.	1 Hour	2½ Hours	1 Day	3 Days	7 Days
Baboons Surviving	RL	4 (12)	4 (6)	4 (12)	4 (12)	3 (9)	3 (9)	3 (9)
	PL	4 (12)	4 (6)	4 (12)	3 (9)	0	0	0
Systemic Arterial Pressure (mean)	RL	130 ± 7	92 ± 14	102 ± 14	91 ± 10			
	PL	113 ± 9	90 ± 0	80 ± 17	88 ± 10			
Pulmonary Arterial Pressure (mean)	RL	9 ± 2	12 ± 1	11 ± 3	8 ± 5			
	PL	13 ± 3	15 ± 2	16 ± 2	13 ± 2			
Central Venous Pressure	RL	−2 ± 2	1 ± 1	−1 ± 2	−1 ± 2			
	PL	−1 ± 4	2 ± 0	2 ± 2	1 ± 0			
Wedge Pressure	RL	3 ± 2	5 ± 1	3 ± 2	1 ± 3			
	PL	3 ± 2	6 ± 1	8 ± 4	5 ± 0			
Cardiac Output (ml/min/kg)	RL	123 ± 13	172 ± 40	133 ± 48	114 ± 40	100 ± 33	133 ± 35	156 ± 44
	PL	163 ± 72	174 ± 25	162 ± 48	164 ± 39			

The first line refers to the number of baboons surviving at the given period. The numbers in parentheses are the numbers of thermal-dye determinations. RL refers to Ringer's lactate-resuscitation; PL refers to Plasmanate-resuscitation. All pressures are in mm Hg and all values are means ± 1 S.D.

barbital anesthesia (1–2 mg/kg). No pentobarbital was used during shock. The animals were not anticoagulated.

The baboons were subjected to deep hemorrhagic shock until their systolic blood pressure fell to 60 mm Hg and were maintained at that level until their resting transmembrane potentials deteriorated to −65 mv.[3,32,37] They were then resuscitated with either 1) Plasmanate (PL) plus their shed blood or 2) Ringer's lactate (RL) plus their shed blood. Twenty-five ml/kg of PL or RL was rapidly infused, supplemented with 44 mEq of $NaHCO_3$. Then the shed blood was infused over a 30-minute period. Throughout the 2½-hour postresuscitative period, enough PL or RL was given to maintain the pulmonary arterial wedge pressures within 5 mmHg of preshock levels. Other indices, such as central venous pressure, urine output, peripheral perfusion, and systemic arterial pressure, were monitored but the wedge pressure was used as the final determinant of fluid replacement. The animals were returned to their cages 2½ hours after resuscitation and were restudied 1 day, 3 days, and 7 days later.

Pressures were measured during the time periods indicated in Table 1; thermal-dye extravascular lung water (EVLW) and cardiac output were obtained during the periods shown in Table 2. Gravimetric EVLW was determined when the animals died. Membrane potentials and skeletal-muscle biopsies, obtained before shock and 2½ hours, 1 day, 3 days, and 7 days after resuscitation, were used to determine the intra- and extracellular components of the muscle water.[32]

In the second set of experiments, four more baboons were subjected to hemorrhagic shock (to a membrane potential of −65 mv), then resuscitated with RL plus their shed blood, and deliberately killed 2½ hours after resuscitation to determine their gravimetric lung waters. Two baboons and one Rhesus monkey served as controls. These animals were tranquilized and anesthetized in the same manner as the other animals except that they were not subjected to shock. They were killed to determine their gravimetric lung waters.

In vivo, the EVLW was measured by using the thermal-dye technique[8,15,26] (Figs. 1 and 2). Three separate injections of 5 ml of ice-cold indocyanine green dye were made via the central venous catheter. Simultaneous thermodilution and dye-dilution curves were recorded from the abdominal aorta by means of the thermistor-catheter. Blood was withdrawn from the catheter at 35 ml/min and then reinfused immediately. The observed thermodilution and dye-dilution curves were corrected for time distortion by using function transformations.[10,28] The extravascular thermal volume (EVTV) was computed as the mean cardiac output (thermodilution and dye dilution) multiplied by the difference in mean transit times of the transformed thermodilution and dye-dilution curves. The values for EVTV were accepted as valid only when the cardiac outputs by thermodilution and

TABLE 2. *Severity of Shock as Judged by Various Indices*

	Membrane Potentials (millivolts)	Time in Shock (hours)	Shed Blood (ml/kg)	Fluid Infused (ml/kg)	Ratio of Fluid Infused to Shed Blood
RL	−66 ± 4	3.4 ± 0.6	31 ± 4	99 ± 27	3.23 ± 1.08
PL	−65 ± 2	4.9 ± 1.5	30 ± 7	66 ± 10	2.25 ± 0.63

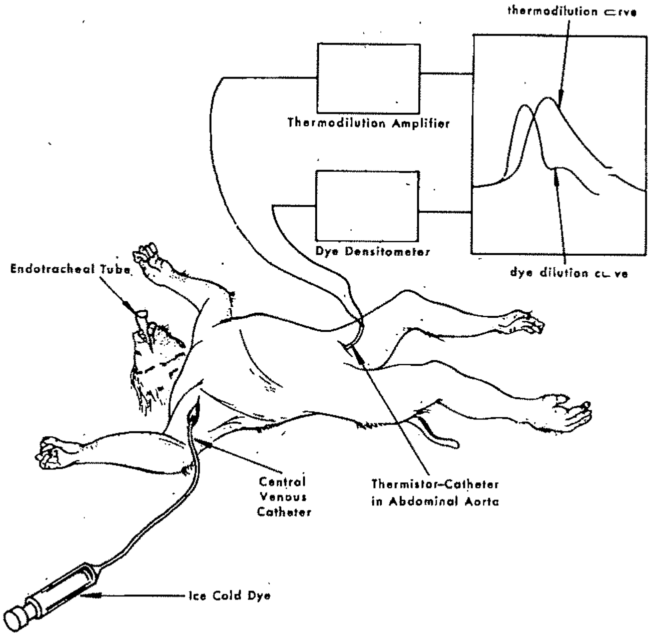

FIG. 1. Placement of catheters and apparatus for thermal-dye determinations of extravascular lung water.

dye-dilution agreed within 20%. A program for a Hewlett-Packard model 9810 A desk-top calculator was developed for the computations. The values for EVTV were divided by 1.15 to give values for the EVLW. This correction was made because in a previous day, the EVTV, was found to be larger than the gravimetric EVLW by a factor of 1.15.[14]

In the animals deliberately killed, lung composition was determined by a modification of Pearce's gravimetric method.[20,27] ^{125}I-labelled albumin (20 microcuries) and 5000 units of heparin were injected intravenously. Exactly 15 minutes later, 60 mg of pentobarbital was given and the chest opened. Both lung hilae were clamped and 20 ml of blood withdrawn from the abdominal aorta. The lungs were excised, weighed, homogenized in a blender with added distilled water, and the homogenate centrifuged. Alliquots of systemic arterial whole blood, homogenate, and supernatant were dried to constant weight at 80 C. Hemoglobin levels were determined in the whole blood and in the supernatant. The supernatant hemoglobin was determined by measuring the peroxidasic activity of free heme pigments under specially buffered conditions. This method was reproducible and sensitive to hemoglobin concentrations of. 5 mg %. ^{125}I-gamma activities in the homogenate and blood were determined on a Packard Auto-Gamma Scintillation Spectrometer. The amount of ^{125}I-labelled albumin injected and the volumes of material counted were small enough to make efficiency and coincidence negligible.

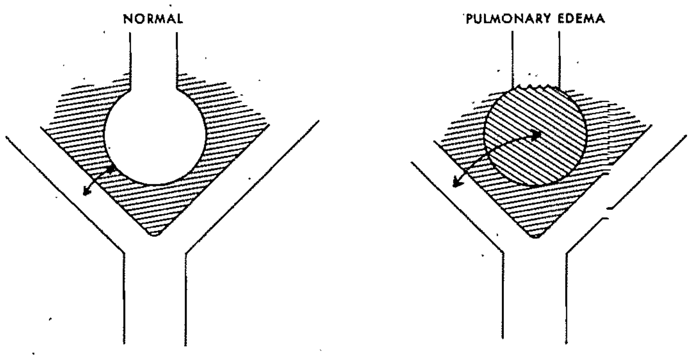

FIG. 2. Caloric distribution as a function of extravascular lung water. The arrows represent diffusion of calories throughout the lung parenchyma following injection of cold dye in the superior vena cava. The diagrams represent an alveolus with surrounding pulmonary interstitium and blood vessels.

The formulae used to determine lung composition were:

$$\text{Blood Weight} = \frac{\text{Hb super}}{\text{Hb blood}} \times \frac{\%\ \text{H}_2\text{O in homo}}{\%\ \text{H}_2\text{O in super}} \times \text{Weight of homo} \qquad (1)$$

$$\text{Blood H}_2\text{O} = \%\ \text{H}_2\text{O in blood} \times \text{Blood Weight} \qquad (2)$$

$$\text{Total Lung H}_2\text{O} = \%\ \text{H}_2\text{O in homo} \times \text{Weight of homo} - \text{added H}_2\text{O} \qquad (3)$$

$$\text{EVLW} = \text{Total Lung H}_2\text{O} - \text{Blood H}_2\text{O} \qquad (4)$$

$$\text{EVDW} = \text{Weight of wet lung} - \text{Blood Weight} - \text{EVLW} \qquad (5)$$

$$\text{PV} = \text{Blood volume} \times (1 - \text{Hct}) \qquad (6)$$

$$\text{AV} = \frac{\text{counts/min/g of homo}}{\text{counts/min/g of blood}} \times \text{Weight of homo} \times (1 - \text{Hct}) \qquad (7)$$

PV is the plasma volume calculated from the Hb-determined blood weights; AV is the volume of distribution of the labelled albumin; EVDW is the extravascular dry weight. Hct is the hematocrit of systemic arterial blood with no correction for trapped plasma. The specific gravity of blood and homogenate was taken as unity. No correction was made for the pulmonary hematocrit.

The statistical comparisons were by Student's two-tailed t test and included all values from the thermodilution and dye-dilution cardiac outputs and all values from the thermal-dye EVLW's. The distributions of the points tested showed no significant skewness nor kurtosis. When variances differed significantly, mean differences were tested by Cochran's weighted t prime.[34] Linear regressions were by the method of least squares. All values in the tables, graphs, and tests are means ± 1 standard deviation (S.D.).

TABLE 3. *Summary of the EVLW Data in Eight Baboons Comparing Resuscitation with RL and PL*

		Study Period						
		Before Shock	Immediately After Resus.	1 Hour	2½ Hours	1 Day	3 Days	7 Days
Baboons Surviving	RL	4 (12)	4 (6)	4 (12)	4 (12)	3 (9)	3 (9)	3 (9)
	PL	4 (12)	4 (6)	4 (12)	3 (9)	0	0	0
EVLW (ml/kg)	RL	5.7 ± 0.9	6.2 ± 0.5	5.3 ± 2.0	5.2 ± 1.5	7.3 ± 2.4	5.6 ± 0.6	6.1 ± 1.7
	PL	4.9 ± 1.2	5.3 ± 0.9	7.7 ± 4.2	6.3 ± 0.6			
Significance		NS	NS	NS	NS			
Change in EVLW from control (ml/kg)	RL		0.4 ± 0.6	−0.2 ± 1.5	−0.5 ± 1.2	1.4 ± 1.8	−0.3 ± 0.9	−0.3 ± 1.6
	PL		−0.4 ± 0.7	2.9 ± 3.9	1.4 ± 0.8			
Significance			NS	$p < 0.05$	$p < 0.001$			

All values are means ± 1 S.D. NS refers to not significant.

Results

Table 1 summarizes the hemodynamic data for the four baboons resuscitated with Ringer's lactate as compared with the four resuscitated with Plasmanate. The systemic arterial pressures were higher in the RL- group before shock ($p < 0.05$). The pulmonary arterial pressures immediately after resuscitation and the cardiac outputs 2½ hours after resuscitation were significantly different ($p < 0.05$) in the two groups, but not significantly different from their own preshock values.

Table 2 summarizes the data concerning the severity of shock in the two groups. There were no significant differences in the membrane potentials, time between hemorrhage and resuscitation, amount of blood lost, amount of fluid infused, nor in the ratio of fluid infused to blood lost. The PL- group required a total of 66 ml/kg of PL as compared with a total of 99 ml/kg of RL in the RL- group. Relatively little PL was needed initially in resuscitating the animals. Maintenance of the wedge pressures over the subsequent 2½ hours, however, required a constant PL- infusion. The RL- animals required more volume initially but subsequently required very little to maintain their wedge pressures.

Table 3 and Figure 3 summarize the EVLW data in the same eight baboons. The first line presents the data in ml/kg. No significant differences occurred between the two groups. The data are more meaningful, however, when the postshock EVLW in each animal is expressed as a change from its own preshock EVLW. This allows each animal to serve as its own control. Expressed in this way, several differences emerge. By 1 and 2½ hours after resuscitation, the PL- animals had accumulated enough EVLW to constitute interstitial pulmonary edema.* The change in the EVLW in the PL- animals was significantly greater than in the RL- animals. The EVLW's in the RL- animals on the days following shock were not significantly different from their own preshock EVLW's.

All four of the PL- animals died by the first day, but only one died a clear-cut pulmonary death. This animal died 2 hours after resuscitation and autopsy showed death was caused by fulminant pulmonary edema and wet heavy lungs. The gravimetric EVLW was 14.2 ml/kg, an increase of 9.2 ml/kg over the preshock EVLW. Expressed as ml EVLW/g extravascular dry weight, the gravimetric EVLW was 8.9. Although the three other PL- animals had increased lung water, they were well enough to be returned to their cages. However, they were all dead by the next morning. Their lungs, on gross examination, were wet but probably not wet enough to account for their death. Their gravimetric EVLW's were 6.3 ± 0.9 ml/kg or 4.7 ± 0.6 ml/g EVDW. For the blood hemoglobin and hematocrit, the values from the previous day were used. The delay in carrying out the

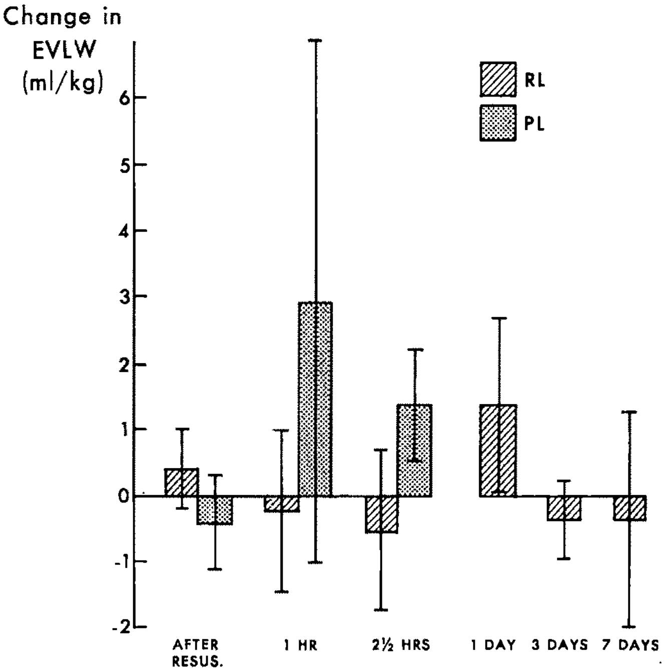

FIG. 3. Extravascular lung water (EVLW) as ml/kg change from pre-shock values. Ringer's lactate versus Plasmanate-resuscitation. Means ± 1 S.D.

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* An increase in EVLW of 1–2 ml/kg is associated with marked interstitial edema which can then lead to fulminant pulmonary edema.[36]

TABLE 4. *Lung Composition in Normal Primates and in Primates Deliberately Killed 2½ Hours After Resuscitation from Shock*

	Species	TLW	EVLW (ml/kg)	EVLW (ml/g EVDW)	Blood Weight (g/kg)	Blood Weight (g/g EVDW)	Blood Weight (% of total lung weight)	PV (g/g EVDW)	AV (g/g EVDW)	AV/PV
Control	Baboon	0.81	4.1	4.3	3.0	3.1	37	2.0	2.6	1.30
	Baboon	0.81	4.0	4.0	1.9	1.9	28	1.3	2.0	1.53
	Monkey	0.80	2.0	4.[illegible]	1.1	2.4	32	1.3	2.1	1.57
		0.81	3.4	4.[illegible]	2.0	2.5	32	1.6	2.3	1.47
		(±0.01)	(±1.2)	(±0.[illegible])	(±0.9)	(±0.6)	(±5)	(±0.4)	(±0.3)	(±0.15)
Shock	Baboon	0.90	12.0	9.[illegible]	1.3	1.0	9	0.7	1.3	1.89
	Baboon	0.84	5.6	5.[illegible]	1.3	1.2	16	0.8	1.9	2.31
	Baboon	0.84	7.3	5.[illegible]	2.2	1.5	20	1.1	2.2	2.01
	Baboon	0.83	4.9	4.[illegible]	1.5	1.4	20	1.0	1.8	1.84
		0.85	7.5	5.[illegible]	1.6	1.3	16	0.9	1.8	2.01
		(±0.03)	(±3.2)	(±2.[illegible])	(±0.4)	(±0.2)	(±5)	(±0.2)	(±0.4)	(±0.21)
Significance		NS	NS	NS	NS	$p < 0.02$	$p < 0.01$	$p < 0.05$	NS	$p < 0.02$

TLW is total lung water expressed as per cent of total lung weight. EVLW is extravascular lung water; EVDW is extravascular dry weight; PV is plasma volume determined by the hemoglobin method; AV is albumin volume determined with I-125 labelled albumin. AV/PV is the ratio of AV to PV as an index of extravasation of labelled albumin after 15 minutes equilibration.

gravimetric determinations in this group does not permit any conclusions to be drawn from these data.

Three of the four RL- animals recovered completely and were killed at 7 days. Their gravimetric EVLW's were normal (6.1 ± 1.7 ml/kg or 4.2 ± 1.3 ml/g EVDW). The fourth animal was accidentally killed on day 1 with an overdose of pentobarbital. She appeared well prior to the overdose.

Extravascular lung water was regressed against 1) wedge pressures, 2) pulmonary arterial pressures, 3) central venous pressures, and 4) systemic arterial pressures. These linear regressions were developed in 1) the PL- group, 2) the RL- group, and 3) both groups together. There were no significant correlations.

Table 4 summarizes the lung composition data in the four baboons killed 2½ hours after resuscitation. These data are compared with the data from the three control primates. There was a significant amount of extravasation of the tagged albumin after 15 minutes equilibration in the animals subjected to shock as compared with the controls.

Table 4 demonstrates the importance of determining pulmonary blood weights when doing gravimetric lung water. The blood weights varied from 9% of the total lung weight to 37%. The variation was equally pronounced when the blood weights were expressed as g/kg body weight and when expressed as g/g EVDW.

The EVLW in the control animals had a very tight standard deviation (5% of the mean) when expressed as ml/g EVDW. When expressed as ml/kg body weight, the standard deviation was 36% of the mean. The monkey contributed the most to this variation.

Figure 4 plots the EVLW against the extracellular water in the muscle biopsies (expressed as ml/100 grams fat-free dry solids). The correlation was significant ($r = 0.51$, $p < 0.02$). The number of simultaneous determinations of EVLW and muscle biopsies was 24.

Discussion

The two methods used to measure lung water in these experiments differ from those used in other studies of lung water accumulation after shock.

The first method, the thermal-dye technique, is a double-indicator dilution technique. Ice-cold indocyanine green dye is injected in the superior vena cava and simultaneous thermodilution and dye-dilution curves are recorded in the abdominal aorta. The caloric marker (i.e. the negative heat) remains confined to the intravascular and interstitial space in the normal lungs as the air-filled alveoli are good insulators against caloric transfer. On the other hand, the caloric marker will diffuse into alveoli flooded with pulmonary edema because the insulating properties of the air will be absent (Fig. 2).

In a previous study in 36 dogs and 6 baboons, the extravascular thermal volume (EVTV) has been demonstrated to correlate well ($r = 0.93$) with the gravimetric EVLW under a wide variety of experimental conditions.[14] The EVTV averaged 15% larger than the gravimetric EVLW, probably because the EVTV included some of the extravascular dry weight of the lungs and some of the mediastinal structures as well as the EVLW.

The thermal-dye technique gave reproducible results in control animals, animals with overload-induced pulmonary edema, and animals with alloxan-induced pulmonary edema.[14] In contrast, double-isotope dilution techniques have not been reliable over this wide range of pulmonary edema.[9,27] The thermal-dye technique offers other advantages over the double-isotope technique:

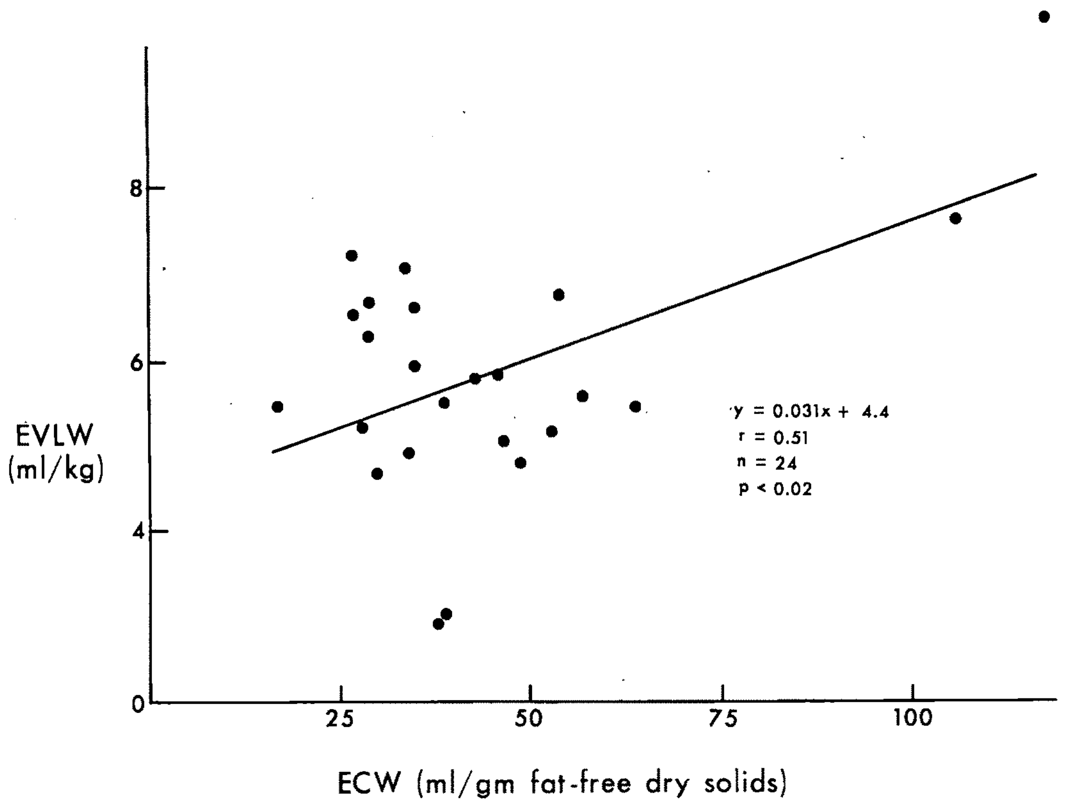

FIG. 4. Extravascular lung water plotted against skeletal muscle extracellular water.

1) no net loss of blood is incurred; 2) determinations can be repeated as often as desired; 3) equipment is small and inexpensive; and 4) the thermodilution and dye curves are inscribed promptly after injection. The disadvantage is that a certain degree of mathematical facility is necessary to work comfortably with the function transformations. Like double-isotope values, the thermal-dye values are reliable only under certain conditions. The recorded curves must have a good signal-to-noise ratio, a good exponential decay, and a clearly-defined recirculation peak of the intravascular marker. In addition, there must be good agreement between the cardiac outputs determined with the intravascular and total water markers. The experimental animals must also be hemodynamically stable.

The second method used to measure lung water in these experiments also differs from those of other experimental shock studies. The pulmonary blood weight was determined by the tissue-hemoglobin technique.[5,7,11,26,27,35] This enabled determination of the pulmonary blood water which allowed the EVLW to be distinguished from the total lung water. In addition, the injection of labelled-albumin permitted direct measurement of the volume of distribution of albumin (AV). This enabled comparison with the plasma volumes (PV) determined from the hemoglobin-determined blood volumes.

There are two essential findings in these experiments: 1) PL-resuscitation was associated with more pulmonary edema than RL-resuscitation; and 2) albumin extravasated readily into the pulmonary parenchyma after shock.

Three objections could be raised against the first finding: 1) the PL- animals were overloaded; 2) the thermal-dye technique inaccurately measured the actual EVLW; and 3) the Plasmanate caused an allergic reaction in the baboons which caused the pulmonary edema. The following considerations support the validity of our conclusion:

1) The amount of solution infused was determined by the pulmonary arterial wedge pressures which, of all the easily-measured hemodynamic variables, best indicates the pulmonary-capillary pressures. There were no significant differences in the wedge pressures between the two groups. Statistically, overloading could not account for the differences found in the extravascular lung waters, regression analysis having failed to demonstrate any significant correlation between the EVLW's and the wedge pressures in the PL- group, RL- group, and in both groups taken together.

2) The thermal-dye determinations of the EVLW were accepted as valid only when they met the criteria previously established as assuring an accurate prediction of corresponding gravimetric EVLW.[14] The values were obtained only after the cardiac outputs and wedge pressures were restored to normal. No measurements were

made during shock itself nor in four baboons hemodynamically unstable immediately after shock (two PL- and two RL- animals).

3) Test doses of Plasmanate were injected subcutaneously, intravenously, and into the conjunctival sacs of the baboons before shock with no adverse reactions. Furthermore, human albumin has been given to baboons before[23] but no allergic reactions have been reported.

The second essential finding in these experiments was the pulmonary extravasation of albumin after shock. Some extravasation occurred in the three control primates, consistent with the findings of Demling and Staub who have demonstrated recovery of significant amounts of labelled albumin from pure pulmonary lymph within 15 minutes of intravenous injection in the normal sheep.[6] Our findings of increased extravasation of albumin after shock are consistent with those of Gump et al who found increased amounts of albumin in the lungs of patients dying of respiratory failure after surgery.[11] Our findings are also consistent with those of another study by Gump et al in which analysis of three simultaneous indicator-dilution curves demonstrated leakage across the pulmonary capillary membranes in patients with respiratory failure.[12]

In comparing volumes of distributions of a labelled substance in animals after shock with control animals, two errors can arise: 1) extravasation[5] or sequestration[16] of red cells after shock would make the calculations of the hemoglobin-determined blood volumes and the derived plasma volumes (PV) larger than they should be; and 2) fifteen minutes equilibration time for the labelled albumin may be insufficient in animals which have been subjected to shock, making the volume of distribution of the albumin (AV) smaller than it should be. Errors of these sorts would *decrease* the ratio of AV to PV. The ratio in this experiment, however, was *increased*.

Several other points of interest emerge from these experiments.

1) Although the lungs of seven animals were drained thoroughly, still 23% ± 10% of their wet weight was blood. Nonetheless, no published studies of gravimetric lung water in experimental shock make a correction for lung blood weight. Such a correction seems essential.[5,7,11,17,20,26,27,35]

2) The gravimetric values showed the least variation in terms of the extravascular dry weight (EVDW), consistent with the findings of others.[18,35] As an aid in converting data expressed in terms of EVDW to data expressed in terms of body weight, the ratio of EVDW (in grams) to body weight (in kg) in this experiment was 1.27 ± 0.23 (S.D.) in 14 baboons.

3) The gravimetric lung water data in the three control primates compare well with Staub's data on normal human lungs.[35] In this study, the control EVLW was 4.1 ml/g EVDW; in Staub's, 4.0. Here the blood weight was 2.5 g/g EVDW; in Staub's, 2.1. These similarities seem to show that fluid compartments in the lungs of the subhuman primate might be similar to those of human beings.

4) In this study there was a significant positive correlation between the extravascular lung water and the extracellular water of the skeletal muscle, apparently different from the findings of Gump *et al.*[13]

To extrapolate the findings of these experiments to the clinical situation, Plasmanate should not be used in large quantities in resuscitating patients from deep hemorrhagic shock. Administered albumin crosses out of the intravascular space into the pulmonary interstitium, thereby raising interstitial oncotic pressure and obviating the value of the administered protein. On the other hand, administration of Ringer's lactate in appropriate quantities was not associated with the development of significant amounts of extravascular lung water. Thus from the standpoint of lung water, we feel that Ringer's lactate is superior to Plasmanate in the resuscitation of patients from deep hemorrhagic shock.

Acknowledgments

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DISCUSSION

DR. WILLIAM EVANS NEVILLE (Newark, New Jersey): This paper by Drs. Holcroft and Trunkey is important, not only as to resuscitation from hemorrhagic shock, but also as to open heart surgery where we use large quantities of Ringer's lactate to fill the pump oxygenator.

All of you who deal in trauma realize it is difficult to accrue meaningful data regarding the immediate clinical aspects of restoring hemodynamics in the acutely traumatized, bleeding patient. The exigencies of the moment demand that the priorities which are lifesaving, take precedence, rather than physiologic documentation. For this reason we have resorted to studies during and directly after open heart surgery to document the efficacy of using large quantities of Ringer's lactate, not only as a replacement but as a perfusate.

I would remind you that the patient is actually bled into the heart-lung machine and perfused by controlling the pump for the period of time that the heart is non-functioning. Thus I feel that our observations, both in the laboratory and clinically, are valid and substantiate the data presented by the previous essayist as to the efficacy of using Ringer's lactate alone for the immediate restitution of the circulatory blood volume in patients in hemorrhagic shock.

(Slide) When you prime the pump oxygenator with 2400 cc of Ringer's lactate and perfuse the patient for a period of time, and then at the end of bypass return all of the oxygenator contents to the patient, you will notice that the serum water is markedly increased, and as is the tissue water, as determined from skeletal muscle biopsies. The serum and tissue water are increased further if it is necessary to add more perfusate during bypass. In essence, we are doing exactly to these patients what is done to the individuals in hemorrhagic shock; that is, restoring his circulating blood volume by the reinfusion of Ringer's lactate.

(Slide) In the beginning we were concerned that the excess fluid would result in intracellular edema, however, as you can see from this slide, we believe that it is all extracellular. Actually from our calculations we concluded that intracellular water was decreased slightly in our patients.

(Slide) We also have taken lung biopsies after perfusion, and you will see that the water in the lung is markedly increased, the P value being less than 0.02. Lung biopsies under these circumstances show a certain element of pulmonary edema, both under light microscopy and the electron microscope. However, none of these patients have ever been in pulmonary edema. It may be that the absence of clinically apparent pulmonary edema is because we keep them on a volume respirator for a period of 24 hours, and they diurese rather rapidly.

Admittedly, our methods of weighing the skeletal muscle and the lung and extracting the water are rather crude when compared to the more sophisticated procedures used by the essayists. This is the reason I'm most anxious to learn their technique, so that we can utilize it in our institution, where we see a considerable amount of hemorrhagic shock from penetrating trauma.

Dr. Paul R. Schloerb (Kansas City, Kansas): Having had the privilege of reviewing this manuscript, I am intrigued by the use of the extravascular thermal volume method, which they have worked out very well. It represents a potentially useful development for the evaluation of pulmonary edema in patients.

I'm also impressed by their use of transmembrane potential as an end point in shock. Although it's said not to be statistically significant, the group treated with Plasmanate was actually in shock at a pressure of 60 mM of mercury an hour and a half longer than the group treated with Ringer's lactate.

Measurement of transmembrane potential, as I understand it from the work presented from Dr. Shires' laboratory, represents the insertion of a probe into a single muscle cell, with measurement of the potential. In other words, are these authors asking one cell to tell them how all the other cells of the body are doing, in this rather severe physiologic derangement?

What is the constancy of measurement from cell to cell under these conditions?

Have you employed any other systemic index, such as the blood lactate measurement, to get further information on this question?

Our own studies have used controlled hemorrhage in the rat. (Slide) This has involved the measurement of muscle as well as pulmonary water in large numbers of rats subjected to an estimated 50% blood loss, followed by resuscitation with Ringer's lactate or Plasmanate. Here muscle water is represented as a function of the volume of Ringer's lactate used, in amounts up to 100 ml/kg, with infusion alone or following 50% blood loss.

Although a modest increase of muscle water occurs with Ringer's lactate resuscitation in increasing amounts following blood loss, the increase does not continue in response to increasing amounts of fluid. It plateaus, indicating that the administered fluid goes elsewhere. It doesn't appear to go in the muscle. Therefore, I'm a bit hesitant to accept the data which you will see in the authors' paper, which purports to show that there is a correlation between pulmonary edema, or extravascular lung water, and muscle water.

(Slide) This shows lung water in these rats, here following increasing amounts of either Ringer's lactate or Plasmanate infusions. There is a significant difference between these two types of treatment, with considerably more pulmonary edema following the Plasmanate infusion, as compared with Ringer's lactate infusion. We're delighted to see, of course, that this is confirmed by the present authors.

Dr. Shires and Dr. Moore published an editorial several years ago with reference to Ringer's lactate infusion. The title of this editorial was "Moderation." I would suggest, rather than abandoning Plasmanate which is still a fairly useful substance, that we ought to use it judiciously, and spell "Moderation" in capital letters.

Dr. Frank Gump (New York): The real significance of these studies goes beyond the choice of the best resuscitation fluid to what is an even more important clinical problem. Efforts to mobilize fluids from the lungs has recently become of great concern to surgeons, especially those dealing with critically injured patients. While diuretics represent the usual approach, albumin has recently been considered an important adjunct, because of the oncotic properties that have been described.

The work that has just been presented suggests that this technique may have certain limitations, and that it will be effective only if used in patients where capillary function is still normal. Certainly, it suggests greater care will be necessary in the selection of patients for albumin therapy.

Now, granted that albumin doesn't do what we expect in this study, I'm still somewhat surprised that the animals would actually end up by having more water in the lungs. In thinking about this, I was struck by one feature in the design of the experiment. As you noticed, the resuscitation end point was the pulmonary artery wedge pressure, and this makes perfectly good sense if you are looking at water accumulation in the lung by any gravimetric technique. On the other hand, if you are looking at water accumulation by measuring it with the double indicator dilution method, the flow through the lung is an even more important variable; so that it might be better to use cardiac output as the resuscitation end point.

Not surprisingly, the cardiac output was somewhat higher in the albumin treated animals, and the increased perfusion that would be associated with this might explain why extra water was measured in this group.

I'd also like to ask about the use of a caloric marker as the diffusable indicator. The work we did used tritiated water, which certainly has an advantage in that its extravascular distribution takes place entirely in the pulmonary capillary bed.

Now, if I understand the cold bolus correctly, the extravascular distribution would start from the point of injection and continue right along until the sampling point. This means that it's dependent on the mean transit time or to put it another way, flow velocity. In the animals getting the colloid, the increased viscosity of the blood would certainly be expected to affect flow velocity and this might also partially explain the findings of increased extravascular water in this group.

To conclude, I think this is an important and provocative paper, in that the authors have focused on the restoration of not only the intravascular volume in dealing with shock, but also on the important point about capillary function and interstitial dynamics. Most important of all, this report emphasizes that some consideration must be given to the pulmonary microcirculation, if we are going to use oncotic agents such as albumin in a rational way.

Dr. Richard M. Peters (San Diego): Drs. Holcroft and Trunkey have presented an interesting study which supports the clinical impression that protein containing fluids are deleterious in the resuscitation from shock. The study suggests that increase in the lung water and protein leaks from pulmonary capillaries are inevitable following shock.

In our laboratories, and those at the Naval Hospital under Dr. Virgilio at the Trauma Research Center at U.S. Naval Medical Center, San Diego, we have recently done some studies of the effect of PEEP on pulmonary capillary wedge pressure, PEEP being positive end expiratory pressure. In the normal animal the positive end expiratory pressure above 10 cm of water causes the pulmonary wedge pressure to rise while the left atrial pressure stays normal and cardiac output falls acutely, indicating that there is a block at the capillary level.

This discrepancy can be prevented by making the animal hypervolemic. Hypervolemia may be essential in patients with pulmonary capillary leak and resultant obligatory increase in lung water which require the use of PEEP to maintain oxygenation.

We have done some studies using ^{125}I in a more dynamic method, counting over the lungs of shocked dogs at the same time blood volume is measured to determine that the proportion of the ^{125}I in the blood by difference can estimate how much protein has leaked from the circulation. We have found a modest protein leak with shock, as have these authors.

Recently, we have been interested in whether this leak would be aggravated by hypervolemia, or overinfusion of fluid. (Slide) Fluid infusion equivalent to nine liters replacement in a patient results in a moderate increase in lung counts in the animals, representing some protein leak. The compliance is decreased modestly, but the lung weights at three days are normal. In another group given low doses of oleic acid and subjected to hypovolemic shock, the injury to the capillary is very extensive and the animals get a marked increase in the protein leak from the lung capillary. The compliance falls, and the lung weight is markedly increased. With just oleic acid alone, the results fall between these two groups.

I think our studies support those of Drs. Holcroft and Trunkey; that after shock there is a protein leak from the capillary. Since we feel it is probably going to be necessary in most of these patients to have them hypervolemic, I wonder if the authors have any opinion about the effect of excessive Ringer's lactate on this protein leak. Will it aggravate it, or will it not aggravate the leak?

In other words, how much is the leak the effect of increasing the pulmonary vascular volume, as compared to just the injury from the shock period?

DR. FRANCIS D. MOORE (Boston): I would warn that "Plasmanate" in the baboon or human albumin in the rat, are *heterologous* albumin. They are strong antigens. They were, after all, the basis of the original description of 6-mercapto-purine, from which azothioprine was developed, and the whole transplant era evolved. It came from the Swartz-Damashek work on heterologous serum albumin. We simply cannot transfer findings of the heterologous protein to the situation of the *human* albumin in *man*.

Drs. O'Connor, Morgan and Laks in our department have done work like this using the thermodilution catheter in man. With hemodilution either for open heart surgery or total replacement of the hip, our findings are the exact reverse. When albumin or "Plasmanate" is added, in moderation, there is less lung water, and there is much less pulmonary shunting. When nothing but Ringer's lactate is used, there is more water in the lung and a bigger shunt.

DR. JAMES W. HOLCROFT (Closing discussion): Dr. Neville, we hope to publish more details of the thermal-dye technique in the near future. Dr. Schloerb asked about the membrane potentials as an index of severity of shock. The potentials are taken from a fresh group of cells at each determination, and each time the potential is determined a whole group of cells is sampled. The technique is very reproducible and, we feel, gives a good clinical and experimental endpoint to the depth of shock, better than the length of time spent in shock. For example, four animals had a cardiorespiratory arrest just as we were about to electively resuscitate them; two PL- and two RL- animals. We did not measure lactates, but the arterial blood gases were essentially the same in the two groups. There was no correlation between the length of time in shock and the amount of pulmonary edema. The two PL- animals with the most edema were in shock for a relatively short time; for 3.2 and 4.3 hours, respectively.

With respect to the correlation of lung and muscle water (Fig. 4), we would only suggest that there is an underlying mechanism that governs the accumulation of water in these two tissues; the differences are probably greater than the similarities.

We agree with Dr. Schloerb's comments about moderation with respect to Ringer's lactate resuscitation.

Dr. Gump asked if the thermal-dye technique is reliable with varying cardiac outputs. We have found it reliable in previous experiments in dogs. As long as it is used under the conditions of these experiments, it does not vary with the cardiac output, pulmonary artery pressure, wedge pressure, nor central venous pressure. In this regard, the thermal-dye technique has proved more reliable than the double-isotope technique. We have no reason to think that serum protein concentrations affect the thermal-dye measurements—some of our early dog studies used massive hemodilution with no effect on the thermal-dye measurements.

Dr. Peters asked if the pulmonary capillary pressure affects the albumin leak. We know the pulmonary artery pressures and we know the wedge pressures, but we don't know the pressures that are most important—the capillary pressures. Thus we cannot answer his question.

Dr. Moore asked about allergic reactions. Test injections of Plasmanate intravenously, subcutaneously, and into the conjunctival sac of all these animals gave no reactions of any sort. Dr. Moore also mentioned that albumin administration decreased lung water in his patients undergoing cardiopulmonary bypass. We would agree since his patients were not in shock. Our point was that in deep hemorrhagic shock, something happens to capillary membranes, or to microvascular forces, so that extravasation of albumin increases. We would not argue about using albumin-containing solutions in patients who are stable hemodynamically and have not been in shock.

Complete Left Ventricular Bypass With a Paracorporeal Pump:

Design and Evaluation

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JAMES H. DONACHY, WINFRED M. PHILLIPS, Ph.D., DONALD L. LANDIS,
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A multidiscipline group was established at The Pennsylvania State University to design and evaluate mechanical circulatory assist devices and the artificial heart. The group has designed a left ventricular to aortic assist system which consists of a sac-type pump, a synchronization unit, a pneumatic power unit, and appropriate monitoring apparatus. The assist system has been evaluated for long-term circulatory assistance in a series of ten calves. The assist pump was placed in the paracorporeal position. The longest period of continuous pumping was over eight months. The last four calves have had synchronized assist pumping which has permitted prolonged ventricular decompression and assist pump flow rates as high as 10 L/min. Three of these four calves had no evidence of thromboemboli. Additional animal studies will be required before clinical use of such an assist pump system can be safely undertaken.

THE RECENT, widespread use of intra-aortic balloon pumping in the treatment of cardiogenic shock has provided clinical validation of the concept that mechanical circulatory assistance can restore adequate hemodynamics when optimal pharmacologic means have failed.[5,14] However, this relatively non-invasive form of mechanical circulatory assistance provides minimal, albeit at times adequate, assistance to the failing heart.

From the Department of Surgery, College of Medicine,
the College of Engineering, and
The Milton S. Hershey Medical Center,
The Pennsylvania State University,
Hershey and University Park, Pennsylvania

Other forms of mechanical circulatory assistance are urgently needed that will relieve the heart of a major part of its work and provide better support of the circulation. Left atrial to aortic bypass fulfills these criteria. However, *maximal* reduction in left ventricular work requires ventricular decompression, not readily obtained with left atrial bypass.[8,10] Left ventricular to aortic bypass with proper synchronization of the assist pump can provide maximum support of a failing left ventricle.

This report describes the organization of a broad-based, physician-engineer-veterinarian group founded to develop and evaluate mechanical circulatory assist and artificial heart devices. The design, evaluation, and results of a left ventricular to aortic assist system designed to provide maximum left ventricular support will be discussed in detail.

Organization

The circulatory assist group is composed of faculty members, graduate students, and undergraduate students of the College of Medicine and the College of Engineering of The Pennsylvania State University. One faculty member of the Department of Surgery, College of Medicine serves as Director while a faculty member of the Department of Mechanical Engineering is Co-Director. A full time research engineer with extensive biomedical experience serves as a coordinator between the two colleges.

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A plastics fabrication shop and a machine shop have been established that are completely dedicated to fabrication of mechanical circulatory assist devices. Virtually all components of the assist system are fabricated at The Pennsylvania State University, (i.e.: pumps, valves, synchronization unit, and power unit).

A variety of expertise is provided by other disciplines (i.e.: aerospace engineering, electronic engineering, and veterinary medicine). At the time the group was established in 1970–71, its members provided a total of thirty years of experience in the area of development of mechanical circulatory assist devices.

Assist System Design

The left ventricular to aortic assist system that has been designed and evaluated consisted of a sac-type pump with an inlet and outlet cannula, a pneumatic power unit, a synchronization unit, and appropriate monitoring apparatus.[9] The sac-type pump consisted of a flexible segmented polyurethane* sac contained within a thin, vacuum formed, polycarbonate shell (Figs. 1, 2). The sac had a wall thickness of 0.635 mm with an increase to 1.016 mm in the area of the outlet valve. The sac had a smooth, seam-free inner surface. Ball-type valves were an integral part of the inlet and outlet ports of the pump. The lightweight pump was designed to be placed in the paracorporeal position, alongside of the left chest of the calf (Fig. 3). Blood was drained from the left ventricular apex through a 1.9 cm inside diameter, wire reinforced, segmented polyurethane cannula (Fig. 4). The pump outflow tube was similarly fabricated. However, an 18 mm woven Dacron graft was bonded to this tube for anastomosis to the descending thoracic aorta. The external surfaces of both cannulae were covered with nylon velour. Special attention was taken to provide a smooth junction between the inlet port of the pump and the ventricular (inlet) cannula. The inlet port of the pump had the same inside diameter as the inlet cannula. The cannula slid over a taper fitting of the inlet port. This cannula was held in place with a locking nut, which also served as an antipulse ring. A similar design was employed on the outlet port of the pump.

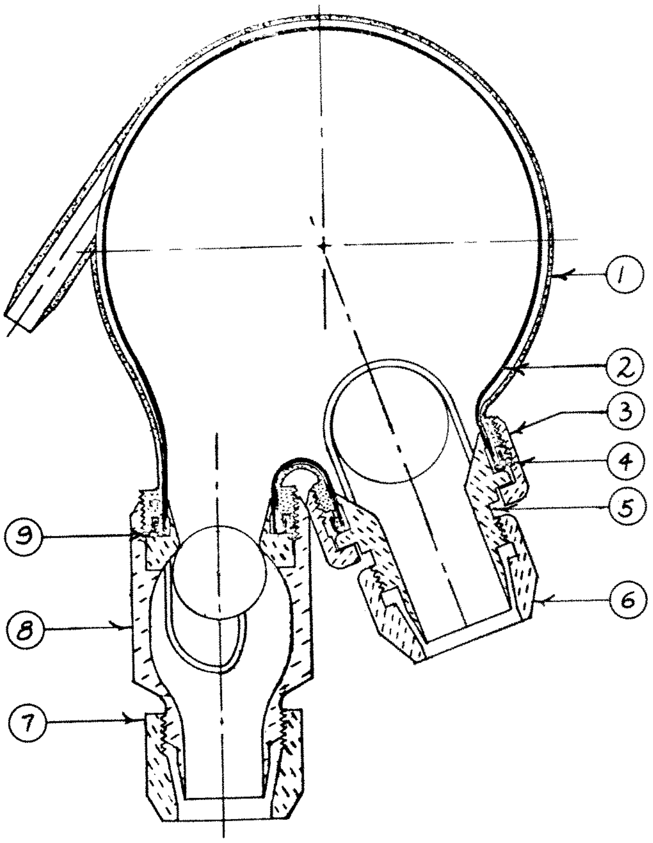

FIG. 1. An engineering drawing of the assist pump. 1. Polycarbonate shell. 2. Segmented polyurethane sac. 3. Inlet connector union nut. 4. Seal ring. 5. Inlet valve. 6. Inlet locking nut. 7. Outlet locking nut. 8. Outlet valve. 9. Seal ring.

The pump was powered by a pneumatic power unit which consisted of a high pressure source, a low pressure or vacuum source, and a solenoid valve which alternately connected these pressure sources to the pneumatic pump line (Fig. 5). A synchronization unit of our design was employed which sensed the R-wave of the EKG, provided a delay, and then energized the solenoid valve to initiate pumping[7] (Fig. 5). Both the delay from the R-wave and the duration of the pumping cycle were changed automatically according to a preset program as the heart rate varied.

A detailed engineering study of the pump was conducted. The total volume of the unit was 180 ml, while the stroke volume was 90 ml, with the opposite sides of the sac in apposition over a 2 cm diameter circle. The maximum output of the pump was 12.5 L/min with an inlet pressure of 10 cm H_2O and a mean outlet pressure of 100 mm Hg. The pump had a hemolysis index of 0.052 ± 0.011 gm Hb/100 L of blood pumped. The pump has a long-functioning life; units have been operated continuously for many months without evidence of flexion failures or other mechanical breakdown. Detailed flow studies have been conducted using amberlite resin particles as flow tracers[12] (Fig. 6). These studies have indicated good washout in most of the pump. However, the washout in the "apex" of the sac, opposite to the valve ports, is only fair.

During calf studies, continuous monitoring of the left ventricular pressure,* aortic pressure,* and EKG was performed through signal conditioners that were an

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* Biomer, Ethinor Inc., Somerville, N.J.

* Millar Mikro-Tip Catheter Pressure Transducer, Millar Instruments, Inc. Houston, Texas.

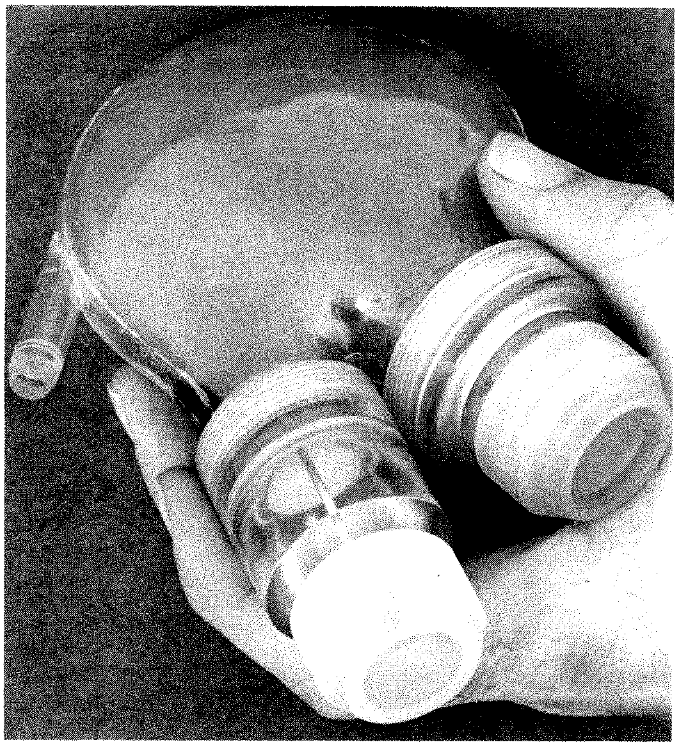


FIG. 2. The left ventricular assist pump as employed in calf experiments. The pump was lightweight and had a maximum output of 12.5 L/min.

integral part of the synchronization unit. These parameters were displayed on a four channel oscilloscope or recorded on a paper writer. Proper adjustment of the synchronization unit insured that the ventricular pressure was reduced to lowest values possible (ventricular decompression) and that the decompression would be automatically maintained even though changes occurred in heart rate. The automatic adjustment of the power unit solenoid operation was based on synchronization parameters observed in calves with ventricular decompression whose heart rates were varied both by drugs and by electrical pacing (Fig. 7).

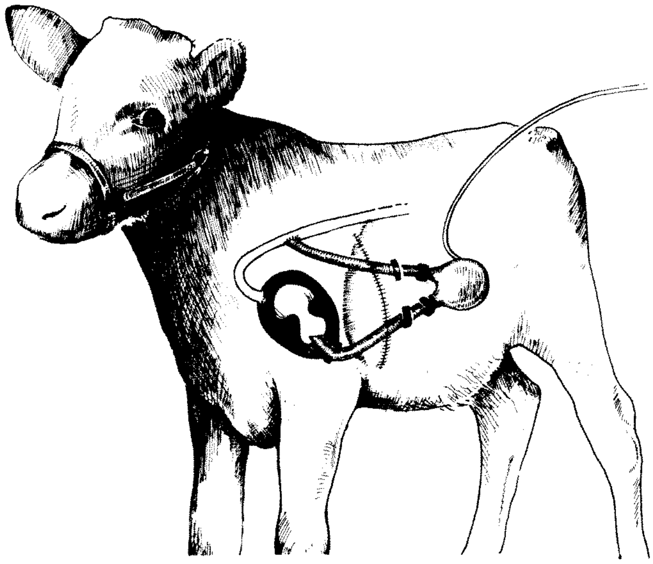


FIG. 3. The assist pump filled from the left ventricular apex and ejected into the thoracic aorta. The pump was positioned on the left side of the calf in the paracorporeal position.

Calf Implantation

Eighty to 90 kg Holstein calves were used. Each calf was anesthetized with halothane and a left 5th inter-

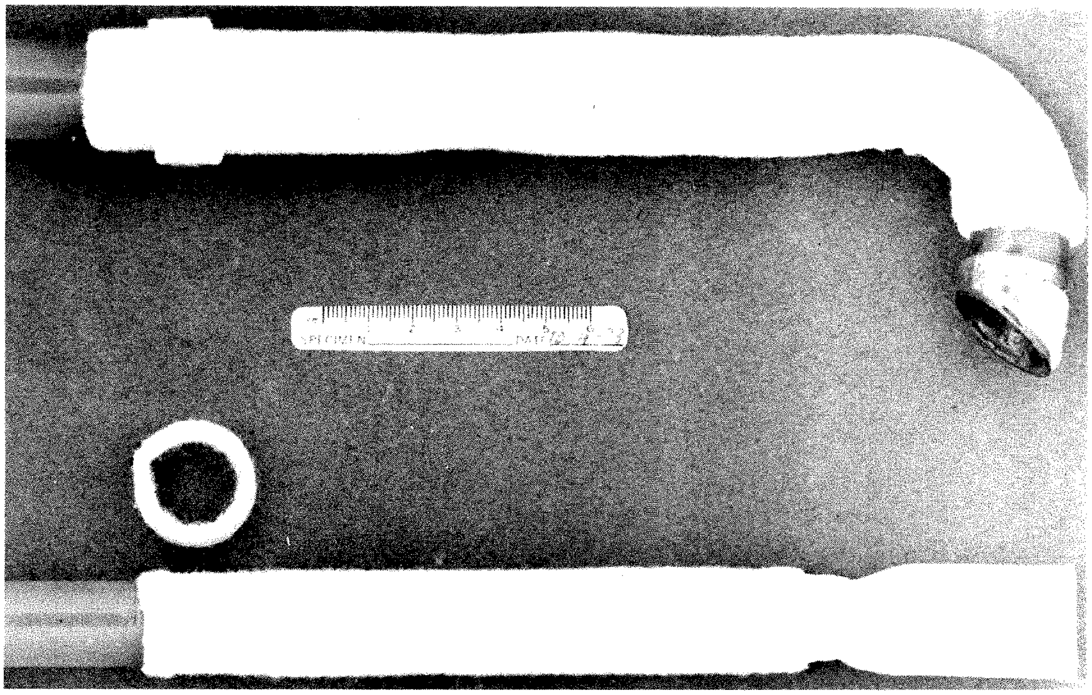


FIG. 4. The cannulae were fabricated of wire reinforced segmented polyurethane. The external surface was covered with nylon velour. A felt ring was positioned at the skin level to aid in securing the tubes. The inlet cannula (top) had a 90° bend and an angled tip. A felt flange limited the depth of insertion into the left ventricle. A Dacron graft was glued to the aortic end of the outlet cannula (bottom).

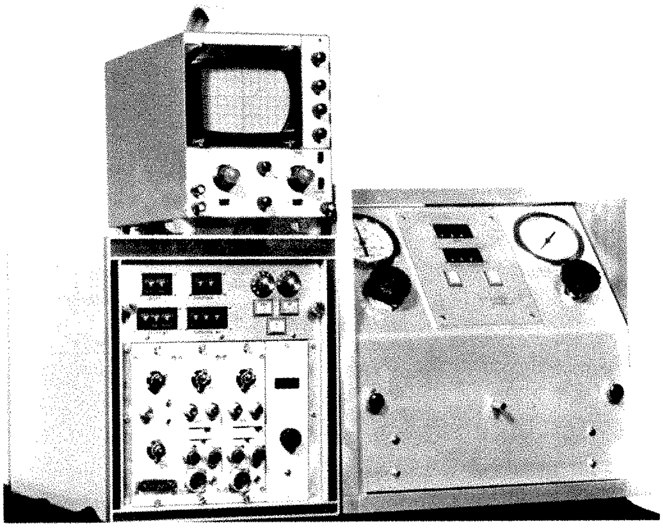
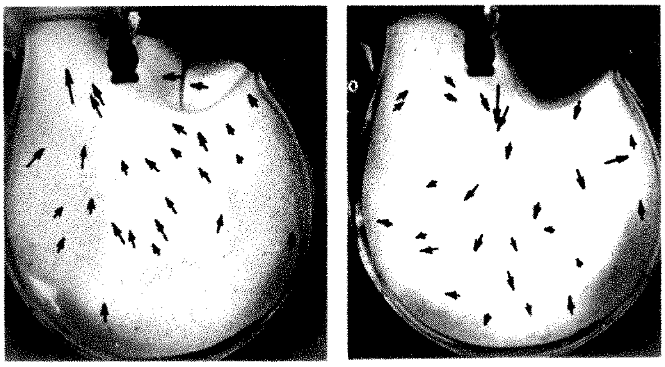


FIG. 5. The power unit (right), synchronization unit and monitoring apparatus (left) used for left ventricular assistance in the calf. The timing parameters of the power unit were programmed by the synchronization unit. The EKG, aortic pressure, and left ventricular pressure transducer signal conditioners were housed in the same unit as the synchronizer. The EKG, left ventricular, and aortic pressure were continuously displayed on the oscilloscope.

costal space incision was performed. The Dacron graft on the aortic cannula was anastomosed to the midthoracic aorta. Heparin was administered as the anastomosis was completed (200 U/kg). The pericardial sac was then opened widely. A felt reinforced purse-string suture was placed in the midportion of the lateral wall of the left atrium. Four felt-backed mattress sutures were placed around the left ventricular apex. A heavy suture was passed through the atrial purse-string and out the apex of the left ventricle. This suture was tied to the obturator of the left ventricular cannula, which had previously been filled with saline. A cruciate, left ventricular apex incision was made and dilated. The dilator was removed and the left ventricular cannula was rapidly inserted into the ventricle (Fig. 8). The previously placed mattress sutures were then passed through the felt rim of the ventricular cannula and tied. The obturator was then released and withdrawn through the atrial purse-string suture. Further detail regarding the insertion of the ventricular cannula has been published elsewhere.[11] The two cannulae were passed through separate incisions in the left 6th intercostal space. The pump was attached and actuation was begun at a low rate.



SYSTOLE DIASTOLE

FIG. 6. Ventricle flow field studied by high speed photography. The length of the arrow indicates the relative velocity of the tracer particle (amberlite resin). Ventricle rate: 75 beats/min., peak power unit pressure: 210 mm Hg, minimum power unit pressure: (−) 10 mm Hg, mock loop atrial pressure: 7 mm Hg, (mean) arterial pressure: 96 mm Hg (mean), flow rate: 8.2 L/min., systole photograph: 165 msec after onset of systole, diastole photograph: 250 msec after onset of diastole.

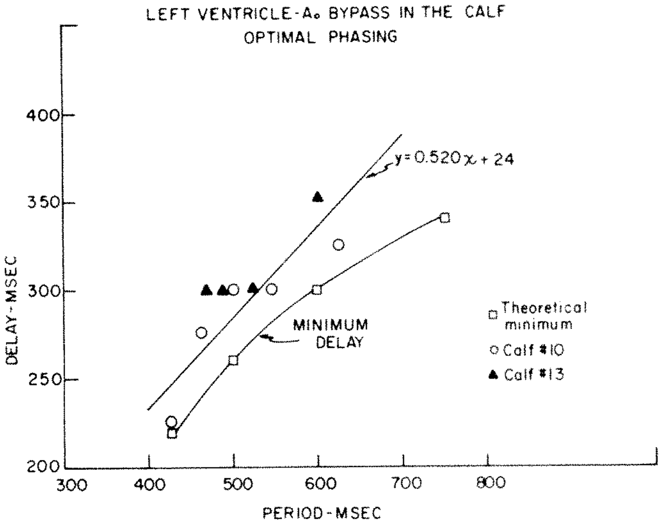


FIG. 7. The synchronization unit automatically increased the delay following R-wave sensing to the onset of assist pump systole as the cardiac period increases. The minimum delay curve was based on theoretical left ventricular pressure tracings. A delay equal to the theoretical minimum insured that the onset of assist pump systole would not occur during ventricular systole. In actual practice, slightly longer delays were required. Data obtained in pacing studies in calf #10 and #13 are shown. The equation representing the actual optimal delay was programmed into the synchronization unit ($y = 0.520\,x + 24$ where x = the cardiac period and y = delay from R-wave).

Continuous monitoring of flows and pressures was performed during left ventricular bypass (Fig. 9). Monitoring of pump flow was performed using an 18 mm electromagnetic flow probe* around the Dacron graft segment of the arterial cannula. Right ventricular output was monitored using a 25 mm electromagnetic flow probe* which encircled the pulmonary artery. A catheter type pressure transducer was fed into the aorta through the internal mammary artery for arterial pressure measurement while a similar transducer was passed across the free wall of the left ventricle to monitor the pressure in that chamber. A Teflon catheter was inserted into the

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* Biotronex Laboratory, Inc., Silver Spring, Maryland.

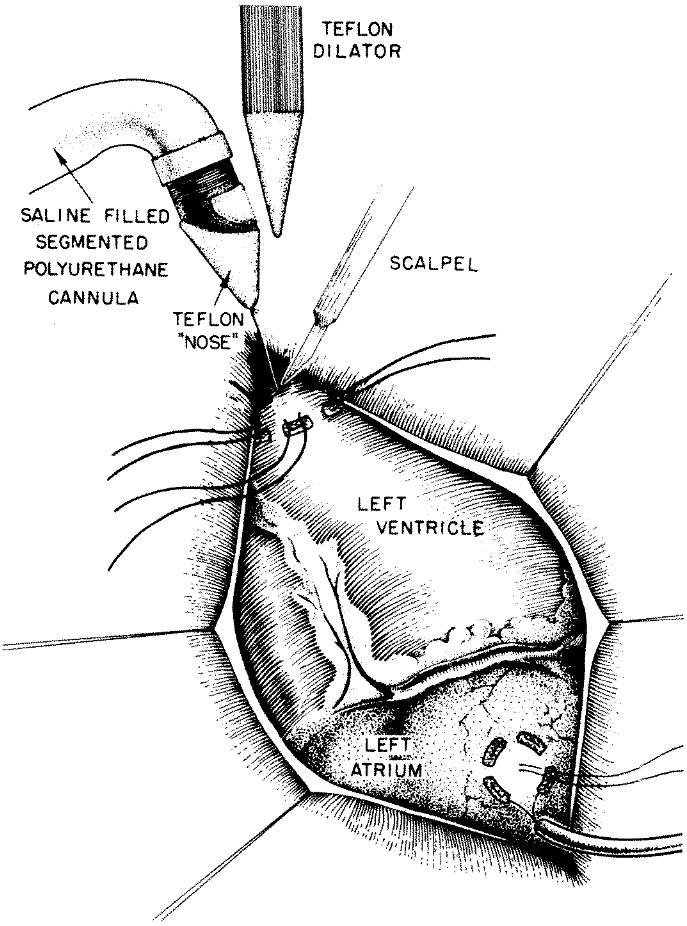

FIG. 8. Left ventricular cannula insertion procedure. An atrial purse-string was placed. Four felt reinforced mattress sutures were placed that encircled the left ventricular apex. A malleable needle was used to pass a heavy suture through the atrial purse-string and out the ventricular apex. This suture was tied to the Teflon "nose" (obturator) of the left ventricular cannula. An apical incision was made and dilated. The saline filled cannula was rapidly inserted into the opening. The previously placed apical sutures were passed through the felt rim of the cannula and tied. The obturator was then released into the left ventricle and withdrawn through the purse-string in the left atrium.

left atrium to obtain blood samples and measure pressure. Two electrode wires were sutured to the left ventricle for continuous EKG recording. All monitoring lines were passed through one chest wall incision and were enclosed within a silicone rubber tube which was then sealed with silicone rubber adhesive.* This tube also had an external cover of nylon velour.

After all monitoring apparatus was in place, the chest was closed. Felt rings were fitted around the pump cannula and the monitoring port. These rings were glued to the tubes with silicone rubber adhesive* and then securely sutured to the skin. The exit ports were dressed with a germicidal ointment† and a sterile bandage. The calf was placed in a restraining cage and maximum pumping was begun. Continuous observation and monitoring was carried out for the duration of each experiment.

The anticoagulation regimen employed after operation consisted of intravenous heparin, 5,000 units every four to six hours to maintain the whole blood clotting time at 20–30 minutes. Heparin was discontinued after five days. Low molecular weight dextran, 20 ml/hr, was administered for 10 days after operation. Coumadin therapy was begun on the fourth postoperative day and was given in a dose sufficient to maintain the prothrombin time at 20–30 seconds.

Blood samples were drawn for determination of hemoglobin, hematocrit, plasma hemoglobin, platelet count, serum sodium, serum potassium, and blood urea nitrogen levels on a daily basis for one week and at weekly intervals thereafter.

Results

Ten calf experiments were performed over a period of about one year. As problems were recognized, modifications were made in the bypass system. Major changes included improved monitoring techniques, improved surface finish of the segmented polyurethane sac, and the use of locking nuts to secure the cannulae to the pump. The use of continuous periods of synchronized pumping was limited to the last four experiments.

In general, the calves stood several hours after return from the operating room (Fig. 10). They ate well and gained weight. They were not bothered by the assist pump. The first six calves in whom the assist pump was used had the device employed continuously for an average of six weeks. The average assist pump flow rate was approximately 3 L/min. The synchronization unit was not employed nor was the left ventricle decompressed. Emboli were a direct cause of death in three of these calves. One calf (see below) died of sepsis, while another calf, in whom pneumonia had been observed at operation, died of respiratory insufficiency in the early postoperative period. One calf died of disconnection of the inlet tube and the pump after two and one-half months of continuous circulatory assistance. Four of the six calves had thrombus in the pump sac at autopsy.

Case Report

This case report represents one of the early experiments and describes the course of the calf that had the longest period of mechanical circulatory assistance in this series.

Calf 5: The assist pump used in this calf did not have an improved blood contacting segmented polyurethane surface. The ventricular and aortic cannulae did not have a velour-covered external surface. Continuous monitoring of flow and pressures was

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[*] Silastic 734 RTV Sealant, Dow Corning Corp., Midland, Michigan.

[†] Betadine ointment, The Perdue Frederick Co., Yonkers, New York.

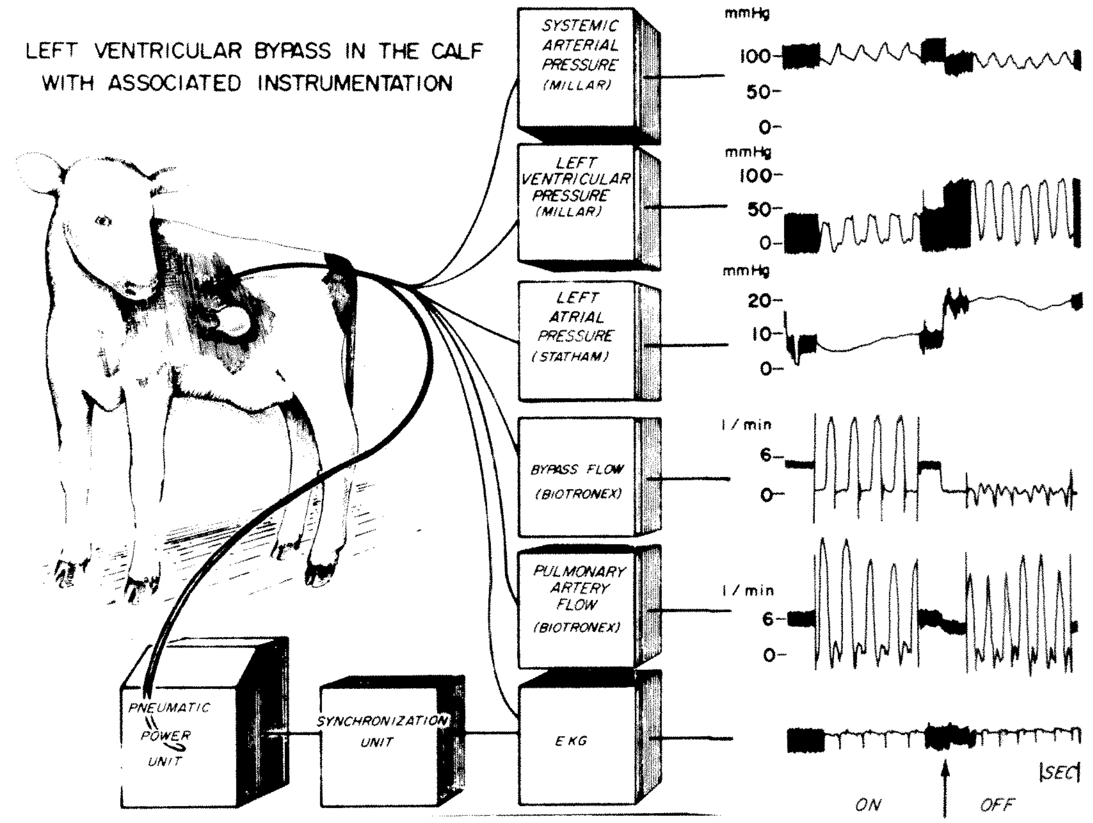
LEFT VENTRICULAR BYPASS IN THE CALF
WITH ASSOCIATED INSTRUMENTATION
SYSTEMIC ARTERIAL PRESSURE (MILLAR)
LEFT VENTRICULAR PRESSURE (MILLAR)
LEFT ATRIAL PRESSURE (STATHAM)
BYPASS FLOW (BIOTRONEX)
PULMONARY ARTERY FLOW (BIOTRONEX)
EKG
PNEUMATIC POWER UNIT
SYNCHRONIZATION UNIT
mmHg
100-
50-
0-
mmHg
100-
50-
0-
mmHg
20-
10-
0-
l / min
6-
0-
l / min
6-
0-
1SEC
ON
OFF

FIG. 9. Continuous monitoring of systemic arterial pressure, left ventricular pressure, left atrial pressure, bypass pump flow rate, pulmonary artery flow rate, and EKG was performed during the assist pump experiments. The recorded parameters are from calf #15. The assist pump system was functioning well with ventricular decompression. The left ventricular peak systolic pressure was 45 mm Hg while the aortic pressure was 110/80 mm Hg. The assist pump was turned off at which point the left ventricular peak systolic pressure and peak aortic pressure were equal at 95 mm Hg. (Power and synchronization settings during first portion of the record were: Peak air pressure 150 mm Hg, minimum air pressure (—) 25 mm Hg. The solenoid valve initiated systole 360 msec after the R-wave and then remained in the systolic position for 180 msec).

not possible and no synchronization unit was available. The pump flow rate was estimated at 3 L/min. The thoracic cannulae were dressed after pump insertion using sterile technique but the dressing was not changed for weeks. The animal became febrile four weeks after operation. The dressings around the thoracic cannulae were removed and purulent drainage was noted. This infection persisted in spite of wound care and antibiotics. The calf appeared healthy and ate well each day. She died of sepsis 8.2 months after pump implantation over which time the calf had grown from 90 kg to 220 kg. Hematologic data are presented in Figure 11. Serum sodium, potassium, and blood urea nitrogen had remained normal. Examination of the pump showed a modest amount of thrombus adherent to the apex of the pump, infection along the course of the thoracic cannulae and evidence of hepatic emboli. The kidneys were free of emboli.

Comment

The last four calves operated upon had the synchronization unit employed. As a result, considerably higher flow rates were possible and ranged from 5.0 to 10.2 L/min. The average period of continuous circulatory assistance was six weeks. One calf died of an incidental intestinal obstruction, another died of pulmonary insufficiency soon after operation, a third of bleeding from a frayed experimental vascular graft, and one died from an infected, occluding "ball valve" type left atrial thrombus (see below). One calf had laminated thrombus in the sac observed after two months of supposedly continuous assist. Careful review of the records of this calf revealed a six-hour period one night where the EKG signal conditioner had failed and the assist pump stopped. The calf sitter had observed this as noted by a brief increase in recorder paper speed but failed to notify anyone. Six hours later, the EKG resumed proper function and the pump was found to be working well during a check at 8:00 A.M. There was thus ample opportunity for thrombus formation in this pump.

Case Report

This case report describes one of these last four experiments.

Calf 15: An improved pump was implanted in this calf. The surface of the segmented polyurethane sac was cast over a smooth silicone rubber dispersion coated form. The transthoracic cannulae were covered with velour on the external surface. Continuous monitoring of a number of cardiovascular parameters was performed and the synchronization unit was employed for over one month during which time the ventricular peak systolic pressure was less than the arterial pressure (Fig. 9). Figure 12 shows hematologic parameters as recorded in this calf. Pump flow was 5 L/min or more at all times. After five weeks of synchronized pumping, the ventricular pressure transducer failed and it was no longer possible to ascertain the presence of ventricular decompression. This calf had a total of 3.8 months of continuous pumping (Fig. 10). Hematologic data are shown in Fig. 12. About one week prior to this animal's death, it became febrile although the transthoracic tubes, which were cleaned and dressed frequently, ap-

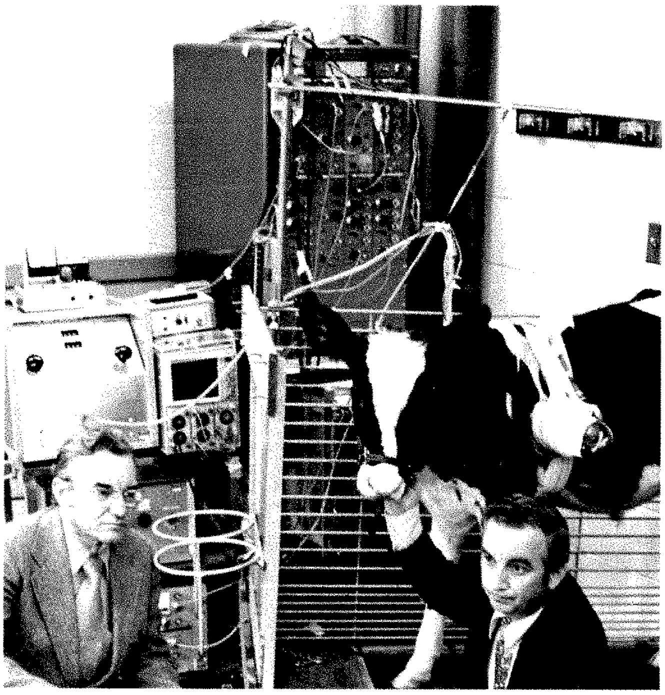

FIG. 10. Calf #15 shown two months after initiation of left ventricular bypass. The calf was alert and comfortable. The power unit, synchronization unit and monitoring equipment are shown in the background.

peared free of infection. Subsequent cardiac examination revealed an infected "ball valve" type thrombus which had originated at the tip of the left atrial pressure transducer and had virtually occluded the mitral valve. The transthoracic cannulae were free of infection. The right ventricle and pulmonary artery were enlarged, findings which were consistent with the occluding "ball valve" thrombus. No abnormalities were detected in the aortic valve or left ventricular myocardium. The pump valves were free of thrombi as were the kidneys and liver.

Discussion

Myocardial oxygen consumption in the normal heart can be reduced fifty percent by left ventricular assistance provided the ventricle is decompressed.[10] The experiments described here are unique in that animals have undergone left ventricular bypass for several weeks to over one month with peak ventricular systolic pressure levels of 40–45 mm Hg while the systemic arterial pressure was at normal levels of 100/60 to 120/80 mm Hg. The aortic valve did not open except during daily tests to verify proper transducer calibration. No aortic valve pathology has subsequently been observed in these calves. Insufficient experience prohibits any statement as to whether prolonged decompression will lead to "disuse" atrophy of the left ventricle. Experience with the intra-aortic balloon pump has demonstrated balloon dependence and the need to "wean" the patient from the balloon pump by assisting the heart on alternate beats.

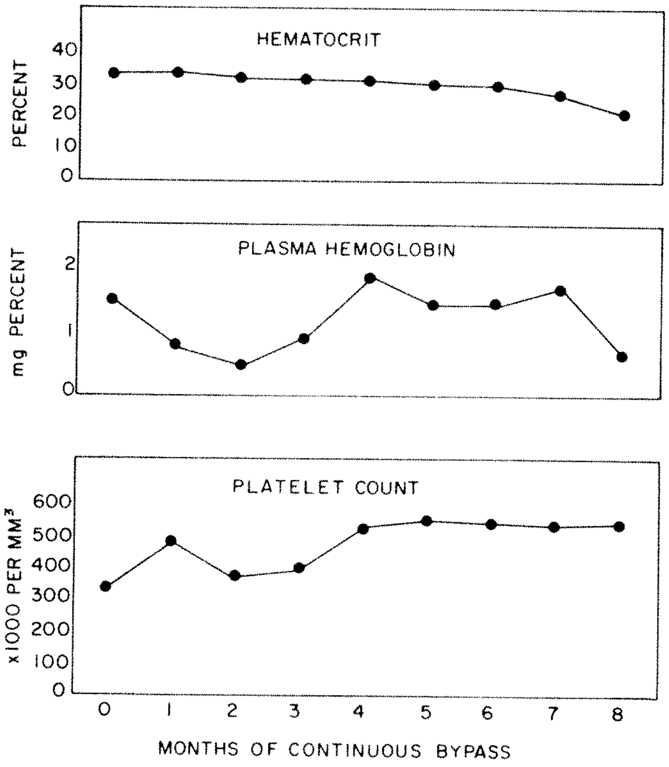

FIG. 11. Hematocrit, plasma hemoglobin, and platelet counts recorded throughout the course of left ventricular bypass in calf #5.

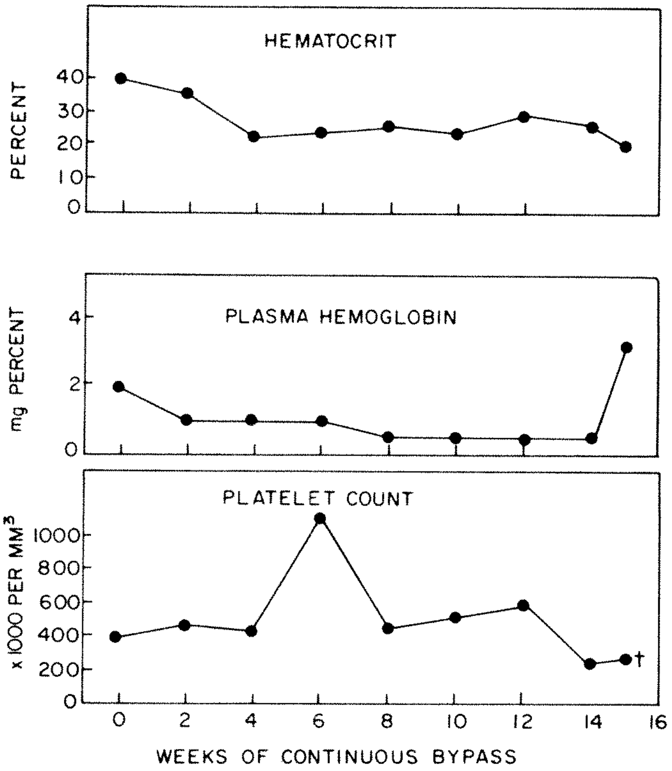

FIG. 12. Hematocrit, plasma hemoglobin, and platelet counts recorded throughout the course of left ventricular bypass in calf #15.

It is possible that such a program will be required to prevent left ventricular atrophy or to permit discontinuance of the left ventricular bypass pump after prolonged assistance.

Thrombus formation within circulatory assist pumps has seriously curtailed clinical application. Thrombus formation is dependent on four factors and all are operant in each experiment. These factors are: 1) pump design, which includes avoidance of stagnant areas, seam-free fabrication, and smooth flow transition areas; 2) blood-material interface, which focuses attention on biocompatible materials, and the use of special linings; 3) flow rate through the device, which must achieve a certain level even in optimally designed pumps with an ideal interface; and 4) modification of the coagulation mechanism, which includes the use of drugs that block an intermediate step in the coagulation process or decrease platelet adhesiveness. The pump described here was designed with particular attention to provide an extremely smooth, seam-free, blood contacting surface, good washout, and a high flow rate. Anticoagulants have been employed in every experiment. Three calves in which these conditions were reasonably well fulfilled had left ventricular assistance without thromboembolic complications. We have not employed fabric or cell lined sacs because of concern regarding delamination and progressive tissue buildup.[1,6]

Few elastomeric materials are available for fabrication of cardiac assist devices. Silicone rubber may be used satisfactorily provided the pump is designed within the limits of the mechanical properties of the silicone rubber.[5] Because of the limitations afforded by silicone rubber, other materials have been evaluated. Segmented polyurethane, first evaluated in the form of roller pump tubing, appears to provide blood compatability of silicone rubber but greatly improved tensile strength and tear resistance.[3] The enlarging experience with this material has provided encouraging information regarding non-reactivity and maintenance of physical properties following prolonged implantation.[2,4] The material possesses a critical surface tension of 28 dynes/cm which is similar to other materials suitable for vascular implantation.[4] When implanted in the vascular system, it is coated with a protein layer having infra-red absorption bands at 1550, 1660, and 3300/cm. The critical surface tension of the sacs as removed from the calves reported herein have ranged from 28–32 dynes/cm. No lipid absorption has been detected up to eight and one half months.

The major limitation to the performance of longer periods of left ventricular assistance with ventricular decompression in calves in this series has been sporadic failure of the catheter type pressure transducers following long-term implantation. A second series of calf experiments is now being planned in which Konigsberg[*] implantable pressure transducers will be employed for the measurement systemic arterial and left ventricular pressure.

Clinical application of the assist pump must wait for additional animal experience. One major concern regarding human use of left ventricular assist pumps is the optimal location of the pump. While such pumps have been placed on the left diaphragm or in the abdomen of the calf, these locations would seem undesirable for clinical application.[1,13] Subcutaneous implantation has been suggested but the sizeable pocket that would be required over the thoracic cage would compromise the nutrition of the skin and skin erosion would be a distinct possibility, particularly in ill "cardiac" patients. We believe that the paracorporeal location as employed by DeBakey and his associates[6] and in the experiments described herein, is the most practical location. Special attention must then be paid to permit a tissue seal around the transthoracic cannulae and to maintain a surgically clean field around the cannulae, much as is done for a subclavian intravenous catheter.[15]

[*] Konigsberg Implantable Pressure Transducer, P-18, Konigsberg Instruments, Inc., Pasadena, California.

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DISCUSSION

DR. HARRIS B. SHUMACKER (Indianapolis): Dr. Pierce and his associates have accomplished a great deal. Among other things, they have demonstrated that long-term left ventricular assistance is feasible in at least one species of animals. They have demonstrated that the device can be constructed to show very minimal, if any, deleterious effects upon the blood elements themselves.

I think, as we move forward toward total cardiac substitution, we run into other problems. My associates and I for a number of years were engaged in such an effort. I'm sorry to say that it is, at the moment, not going on.

But if one aims to implant within the body a total cardiac substitute, then one must indeed deal with size, space, with methods of regulation which are intrinsic in the mechanism itself, and yet sensitive enough to the body needs to maintain a good homeostasis.

One must be certain that one can dissipate the heat of the motivating force, which in our experiments was an electrical motor, and all of our studies led us to believe that these difficult problems are indeed conquerable. All that is required to extend this beautiful study of long-term assistance to total replacement is a lot of hard work on the part of a great many people, and some good original thinking.

DR. WILLIAM S. PIERCE (Closing discussion): One of the most controversial areas in circulatory assistance and in the artificial heart today concerns the lining of the device that is used. About five years ago the use of devices with smooth linings was pretty much abandoned for a variety of flocked or fabric linings. We have never been convinced that the smooth lining was not better. The studies we have performed to date have all employed segmented polyurethane, with as smooth a blood contacting surface as possible.

We believe the circulatory assist system described today provides the maximum form of circulatory assistance. It can, however, be operated in modes which provide lesser degrees of assistance. The use of a paracorporeal type pump permits removal of the device without requiring an additional operation, which is particularly important in ill patients having marginal left ventricular function.

Management of Truncal Valvular Regurgitation

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The presence of significant truncal valvular regurgitation presents a technically difficult and life-threatening challenge during operations for correction of the truncus arteriosus anomaly. The problem was encountered in 19 of 71 patients (26%) who underwent such operations. A simple technique for managing this problem, namely, temporary cusp approximation, has evolved and has proved successful in all 11 patients in which it was used. The indications for replacement of the regurgitant truncal valve have not yet been defined. The suggestion is made that in all but the most severe instances of truncal valvular regurgitation, persistence of the regurgitation postoperatively may currently be preferable to replacement of the valve.

During any open heart operation, attention must be given to preservation of the myocardium. For procedures in which cross-clamping of the ascending aorta is required or is advantageous because of the relative quietness and bloodlessness provided by myocardial ischemia, four methods of protection against irreversible myocardial damage due to ischemia are available: 1) use of only a brief period of myocardial ischemia; 2) perfusion of the coronary arteries by direct cannulation, as in operations on the aortic valve; 3) intermittent release of the aortic clamp to allow coronary perfusion; or 4) cooling of the myocardium. For the repair of complex forms of congenital heart disease, we prefer to release the aortic clamp for a three-minute period every 15–20 minutes (with the whole-body perfusate at 25–30 C). However, significant associated aortic regurgitation precludes this method because, after release of the aortic clamp, most of the perfusate returning from the heart-lung machine through the arterial cannula escapes through the defective aortic valve; this not only reduces systemic blood flow and pressure essentially to nil but also floods the open heart and operative field with blood that overwhelms the removal capacity of the suckers. Thus a vicious combination of cardiac arrest and poor perfusion develops.

Truncal (aortic) valvular regurgitation, a frequently associated complication of persistent truncus arteriosus, poses this technical dilemma. This report deals with the surgical management of patients in whom a significant degree of truncal valvular regurgitation was present at operation and with the description of a preferred technique to maintain myocardial integrity during the repair.

Patients

Since the first successful repair of truncus arteriosus in September 1967,[8] 71 patients with truncus arteriosus (50 of type I, 17 of type II, and 4 of type III)[4] have been operated on at the Mayo Clinic. The patients' ages ranged from 12 months to 19 years (mean, 8 years).

Before operation, the presence of truncal valvular regurgitation (Tr R) could be anticipated by the presence of a typical decrescendo diastolic murmur along the left sternal border and regurgitation of radiopaque medium into the ventricles when injected just above the truncal valve during angiocardiography. However, there was relatively poor correlation between these findings and the presence and severity of Tr R at operation. Thus, among the 71 patients, a diastolic decrescendo murmur had been recorded in 48 and some degree of

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Tr R at operation in 39, but in 20 of these patients the degree of Tr R was mild and did not pose the technical problem that has been described. Among the other 19 patients in whom Tr R was significant (i.e., regurgitation that did cause the technical problem), angiography had led to a diagnosis of significant (i.e., more than mild) Tr R in only 9.

Among the 19 patients with significant Tr R, the truncus valve was tricuspid in 13 patients, bicuspid in 4, and quadricuspid in 2. Slight thickening of the free margin of the cusps was a consistent finding. Poor development or contraction of one or more cusps was noted in five patients, elongation and prolapse of the cusps in one, and calcification of one cusp in one.

Surgical Technique and Results

The surgical technique for correction of truncus arteriosus has been previously described.[8,9,14] The first step is to separate the pulmonary artery (or pulmonary arteries) near its origin from the truncus and to close the resulting truncal defect. During the second step, a longitudinal ventriculotomy is made in the basal portion of the free wall of the right ventricle (Fig. 1). The ventricular septal defect is then closed so that the aorta receives blood only from the left ventricle. The final step is to insert a valved conduit between the right ventriculotomy and the pulmonary artery. This conduit, in our initial experience, was a homograft of ascending aorta and aortic valve, but since November 1972 we have used a prosthetic Dacron conduit bearing a porcine aortic valve (Hancock Laboratories, Inc.).

In the evolutionary management of these 19 patients having a significant degree of Tr R at operation, six different techniques were used, essentially in chronologic sequence.

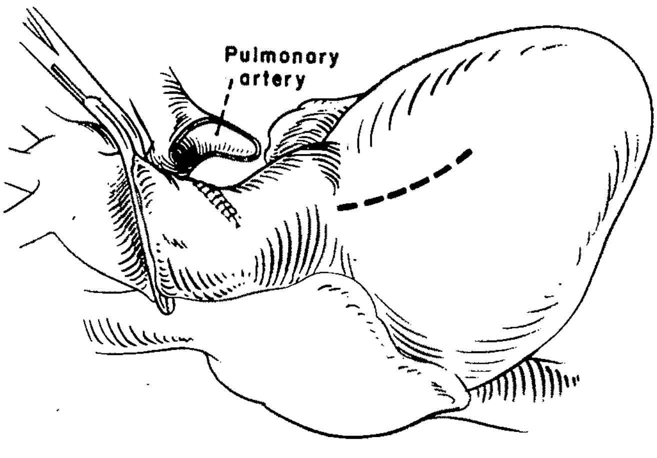

FIG. 1. Repair of truncus. Pulmonary artery was excised from truncus and resultant defect closed. Site of longitudinal ventriculotomy is shown.

1. Replacement of Truncal Valve With a Prosthetic Valve (Three Patients)

The truncal valve was replaced with a Starr-Edwards prosthesis in three patients. The first was a 6-year-old girl. The truncal valve was quadricuspid and severely incompetent; the cusps were thickened and contracted. A no. 7A Starr-Edwards valve was inserted. This patient died, in a state of low cardiac output, on the second postoperative day.

The second patient was an 8-year-old girl who, preoperatively, was found to have a moderate degree of Tr R. At operation, severe Tr R was evident. There were three cusps having thickened and retracted free margins, and the annulus was dilated. The truncal valve was replaced with a no. 8A Starr-Edwards prosthesis. She died on the third postoperative day, in low cardiac output.

The third patient was a 7-year-old boy who, also, had clinical evidence of Tr R. The valve was tricuspid, with elongation and partial prolapse of the cusps. The valve was replaced with a no. 8A Starr-Edwards prosthesis. He survived the immediate postoperative period but died suddenly 2 months later. Postmortem examination revealed dehiscence of the prosthetic valve.

Coronary arterial cannulation and perfusion were established in each of these three patients.

2. Continuous Cross-Clamping of the Aorta Throughout Cardiac Repair (Two Patients)

In two patients, the aorta was cross-clamped throughout the period of the repair. The first patient, a 15-year-old girl, survived the immediate postoperative period, but subacute bacterial endocarditis developed and she died 2 years later. The second patient, also 15 years old, died in low cardiac output during the first postoperative day.

3. Cannulation and Perfusion of the Coronary Arteries Without Valvular Replacement (One Patient)

In a 10-year-old girl, the aorta was cross-clamped soon after the start of cardiopulmonary bypass. The pulmonary artery was excised from the truncus. The left and right coronary arteries were cannulated via the resulting orifice of the aorta. The aortic defect was closed last. This patient recovered uneventfully.

4. Repair of the Truncal Valve (One Patient)

An 11-year-old boy had a bicuspid valve with severe regurgitation. A single silk suture approximated the cusps at each of the two commissures, about 3 mm from the annulus. This completely eliminated the regurgitation through the valve during operation, and the sutures were left in place. The patient did well postoperatively but 1 year later had evidence of moderate Tr R.

5. Maintenance of Competence of Truncal Valve by Digital Pressure (One Patient)

In a 7-year-old boy the truncal valve was maintained competent by finger pressure on the under surfaces of the cusps during periods when the aortic clamp was released, so that the severity of Tr R was temporarily reduced. The patient made an uneventful recovery and was in good condition 8 months after operation, but with evidence of Tr R.

6. Temporary Cusp Approximation

This, the currently preferred technique, will be described in detail.

After the cardiopulmonary bypass has begun, a vent (internal diameter, 0.3 cm [2/16 inch]) is inserted in the apex of the left ventricle and connected to the vacuum source of the heart-lung machine. The temperature of the perfusate is lowered to 28 C. As soon as the heart distends or ventricular fibrillation develops, or when the body temperature reaches 30 C, the aorta is cross-clamped just distal to the origin of the pulmonary artery. During the first period of cross-clamping, the pulmonary artery is excised from the truncus and the resulting aortic defect is closed. Ventriculotomy is then performed. The aortic clamp is released as a right-angled clamp is inserted via the ventriculotomy to keep the truncal valve open until air is evacuated from the aortic root by blood. If much blood continues to return through the valve (Fig. 2) after removal of the right-angled clamp, accompanied by a significant fall in the aortic pressure, the aorta is reclamped. Then, through the ventriculotomy, the center of each cusp of the truncal valve (corpora arantii) is identified, and these are sutured to each other. As this stitch is tied, a plain traction ligature is caught within it (to facilitate its later removal) (Fig. 3). When this is accomplished, the aortic clamp can again be released (usual precaution to evacuate air from the aortic root being taken, as described); in our experience the valve has always then been found to be essentially competent. Thus the usual method for preservation of the myocardium can then be practiced throughout the remainder of repair; that is, restoration of myocardial perfusion for 3-minute intervals every 15–20 minutes.

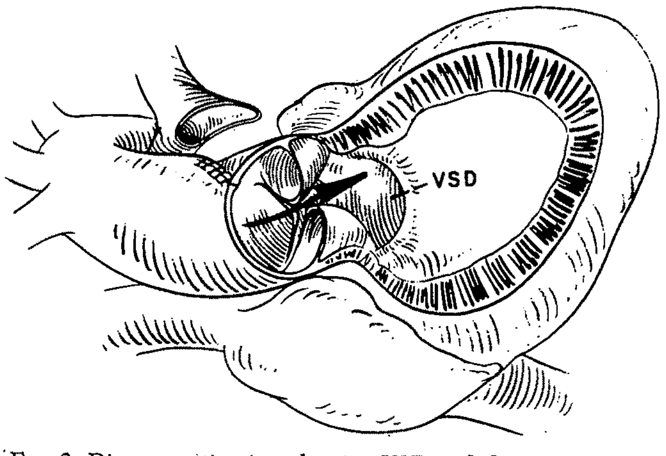

FIG. 2. Diagrammatic view showing VSD and demonstrating prolapsed cusp of truncal valve.

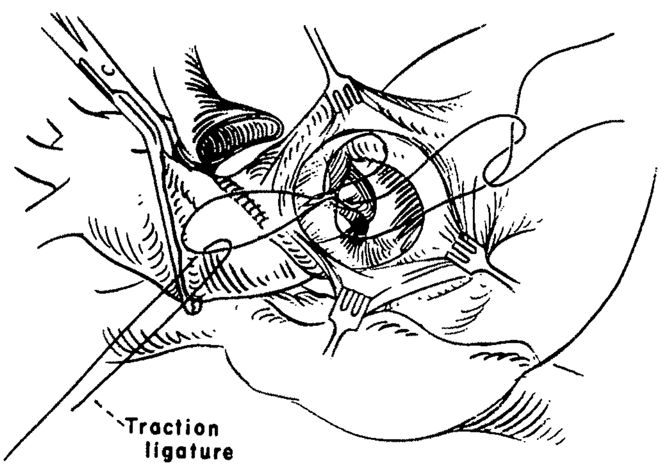

FIG. 3. Truncal valvular regurgitation corrected by temporary cusp approximation. Cusps of truncal valve are sutured to each other. As stitch is tied, plain traction ligature is caught within it to facilitate its later removal.

The ventricular septal defect is then closed except along its superior aspect, where the sutures are placed, but not tied, in order to keep access to the truncal valve (Fig. 4). The anastomosis of the conduit to the pulmonary artery is performed next, and rewarming of the perfusate is begun at the completion of the anastomosis. The aorta is then unclamped and the heart is defibrillated if necessary. After the vigor of the cardiac action seems to have returned to normal, a short additional period of aortic cross-clamping is instituted; during this period the tacking suture in the aortic valve is snipped with sharp-pointed scissors. This step is facilitated by the presence of the traction ligature that was ensnared by the tacking suture (Fig. 5). The aortic clamp is then released for the final time, and aortic regurgitation is thus reestablished (Fig. 6). Now, however, the heart is beating and capable of ejecting the regurgitating volume of blood. In order to minimize the loss of blood through the unclosed superior margin of the ventricular septal defect, a broad-tipped forceps is used to approximate the septal patch to the superior margin of the ventriculotomy as the final sutures in the patch are tied. As this is accomplished, the vacuum to the left ventricular vent is progressively decreased and discontinued. The proximal end of the conduit is then anastomosed to the margins of the ventriculotomy to complete the repair (Fig. 7).

We have used this technique in 11 patients. All 11

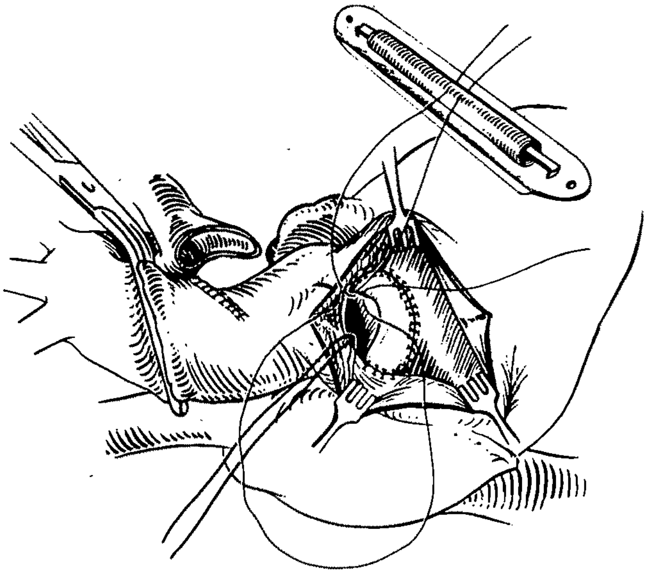

FIG. 4. Preservation of access to truncal valve during closure of ventricular septal defect; the sutures along its superior aspect are placed but not tied.

patients survived the postoperative period. However, one patient (a 13-year-old girl) died suddenly 17 months after operation; presumably death was related mainly to severe residual pulmonary vascular obstructive disease as well as to the residual aortic regurgitation. The remaining 10 patients continue to do well from 1 to 53 months later (mean followup, 9 months).

Table 1 summarizes the early and late results of the techniques for management of Tr R. The technique of temporary cusp approximation has proved successful and the results compare favorably with those of repair of truncus arteriosus unassociated with Tr R.

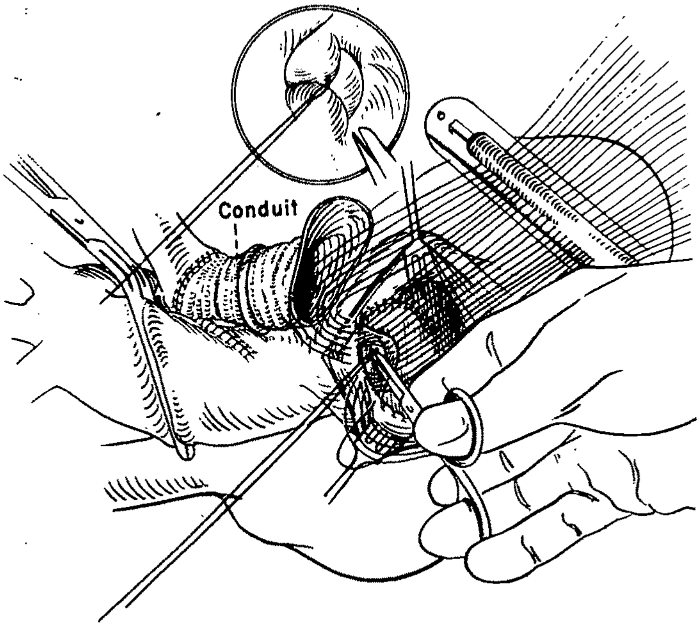

FIG. 5. Removal of tacking suture facilitated by presence of the traction ligature, ensnared by approximating stitch (*inset*).

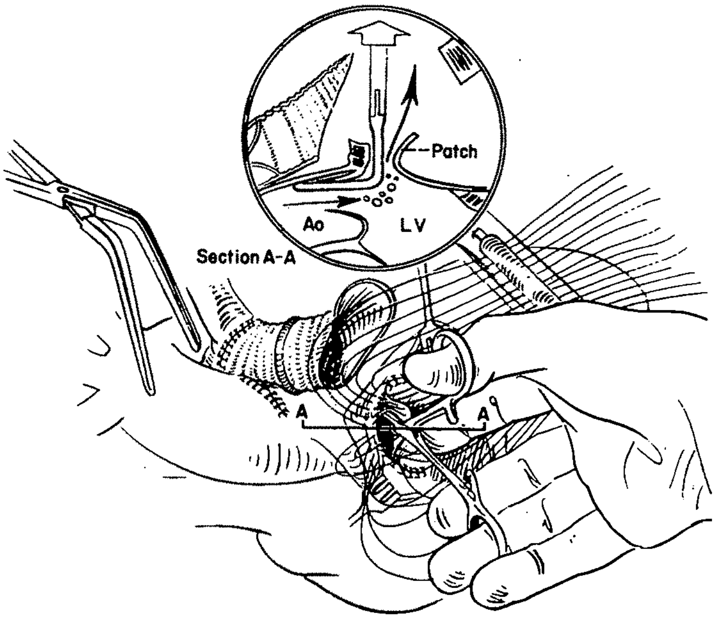

FIG. 6. Final release of aortic clamp. Right-angled clamp makes valve incompetent to eliminate air from the aorta (*inset*).

Discussion

Deformities of the truncal valve were described in the first case of truncus arteriosus reported by Buchanan[3] in 1864. This problem has been studied by several authors.[1,10,11,13] Becker and associates[1] found abnormalities of the semilunar valve in 9 of a series of 14 cases; the abnormalities included prolapse, nodular thickening, and variation in size and number of cusps, as well as im-

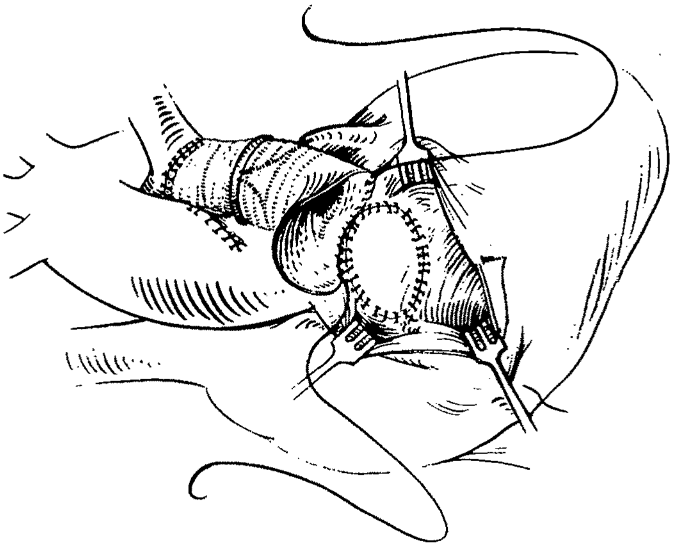

FIG. 7. Completion of repair. Proximal end of the conduit is anastomosed to margins of ventriculotomy.

TABLE 1. *Results of Management of Truncal Valvular Regurgitation*

Surgical Management	Patients	Early Deaths	Late Deaths
Truncal valve replacement	3	2	1
Cross-clamping of aorta	2	1	1
Perfusion of coronary arteries	1	0	0
Repair of valve	1	0	0
Digital maintenance of valvular competence	1	0	0
Temporary cusp approximation	11	0	1
No truncal regurgitation	52	21	0
Total	71	24	3

perfectly supported commissures. Nodular thickening of the cusps was the most consistent change and was related to the presence of increased mucoid connective tissue that may in part have appeared on a developmental basis or secondary to trauma to the cusps. Gelband and associates[6] recently showed that, of a total of 12 patients with truncus arteriosus who died before the age of six months, all 7 with a demonstrable diastolic blowing murmur along the midsternal border during life showed obvious gross and microscopic valvular deformities at autopsy. Thus Tr R, when severe, seems to be a major cause of death during the first 6 months of life.[5,6] Among patients who survive infancy, Tr R remains common: 26% of our patients who came to operation had significant Tr R.

No technique for plastic repair of an incompetent semilunar valve has provided significant long-term success. Two choices remain for the operative management of Tr R: 1) to replace the valve with one of the various available substitute valves or 2) to allow the Tr R to continue after operation in the belief and hope that it will not seriously detract from the benefit derived from correction of the truncus arteriosus anomaly, or at least will allow a better overall result than would replacement of the valve.

The choice between conservative management and replacement of the deformed truncal valve puts a premium on knowledge of: 1) the natural history of Tr R; 2) the relative importance of Tr R in the pathophysiologic aspects of the particular patient; and 3) the long-term result of valve replacement in children with this deformity.

The natural history of Tr R after repair of the truncus is not known. By analogy one could refer to the course of young patients suffering from rheumatic aortic regurgitation. The long period of clinical compensation of these patients is well known. Bland and Wheeler[2] described the clinical course of 87 patients with severe aortic regurgitation (diastolic pressure, <40 mm Hg) under the age of 21 years. They were followed for 20 years after the first attack of rheumatic fever. After 10 years, more than 33% of these patients were still able to lead nearly normal lives; and at the end of 20 years, 25% of them remained in this favorable category. On the other hand, 38% died within 10 years and 56% died within 20 years.

Spagnuolo and associates[12] more recently reported an analysis of the natural history of the condition in 174 similar patients. These authors showed that these patients who have 1) radiologic signs of moderate or severe left ventricular enlargement, 2) two or three major electrocardiographic abnormalities, and 3) abnormal blood pressure constitute a high-risk group; 87% of those patients either died or had symptoms of congestive heart failure or angina within 6 years. Within that high-risk group, patients with a high systolic pressure (>140 mm Hg) and a low diastolic pressure (<40 mm Hg), or both, had the poorest prognosis.

For the patient with such severe Tr R that replacement of the aortic valve would be required if this were the only problem, it is obvious that then valvular replacement should be a part of the operation for repair of his truncus arteriosus anomaly. On the other hand, if the degree of Tr R were less than that which would cause disability or severe cardiomegaly if it were the only abnormality present, it seems likely that replacement of the valve at the corrective operation would at present be unwise. Unfortunately, distinction between these degrees of severity in the associated presence of truncus arteriosus is, at best, an estimate, because radiologic evidence of enlargement of the left ventricle, electrocardiographic evidence of left ventricular hypertrophy,[7] and a wide pulse pressure are common features in truncus arteriosus even without Tr R. Both persistent truncus arteriosus and aortic regurgitation have a similar physiologic effect: they cause volume overloading of the left ventricle.

For these reasons, and until we have more information about the late results of valvular replacement in children and of the late results of patients with and without residual Tr R after repair of truncus arteriosus, we plan to maintain a conservative attitude toward replacement of the truncus valve during operations for the repair of truncus arteriosus—recognizing that, ultimately, reoperation for replacement of this valve may be required in some patients. Only when the most severe Tr R is present, associated with evident gross deformity of the valvular cusps, do we currently elect to replace the truncus valve.

Addendum

Since this manuscript was submitted, two boys (one, 14 years old and one, 6 years old) with truncus arteriosus and associated severe Tr R urgently required operation because of advanced and rapidly progressive cardiac decompensation. In each patient, the truncal (aortic) valve was replaced by a model 1260 Starr-Edwards valve prosthesis, under coronary arterial perfusion. The two boys recovered more slowly than normal, but in each the early result has been excellent.

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DISCUSSION

DR. M. R. DE LEVAL (Closing discussion): I might just mention that all our patients who underwent surgery were over one year of age, with a mean of eight years. According to a recent clinical-pathological study published by Gelband and his associates, truncal regurgitation seems to be a major cause of death during the first six months of life. We have no experience with these patients, and an aggressive approach might have to be considered in some of these infants.

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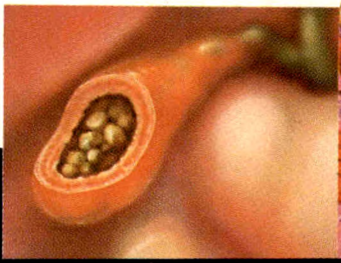
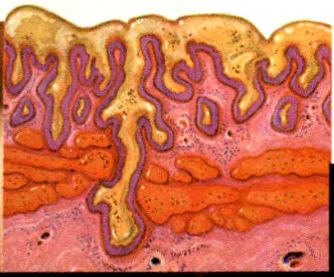
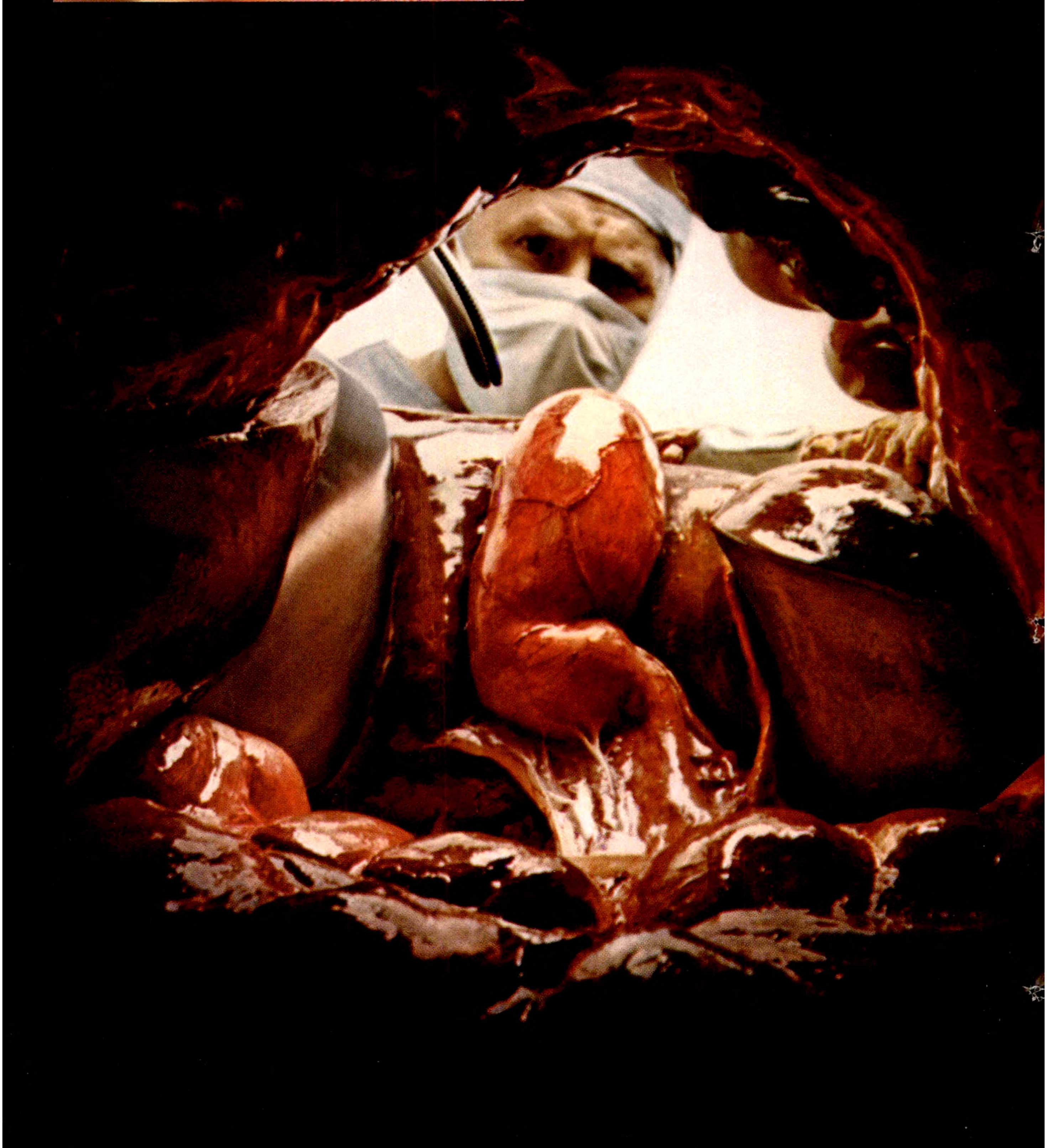


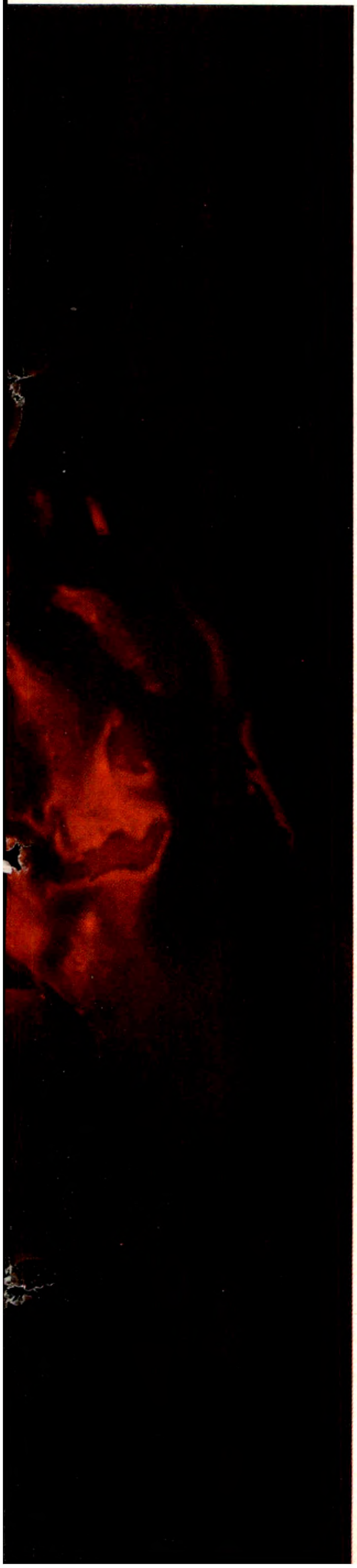


1. Artist's conception of cutaway view of gallbladder containing stones which, by causing irritation of the organ's interior wall and restricting biliary flow, may play a role in the repeated episodes of inflammation and infection associated with chronic cholecystitis.

2. Artist's conception of microscopic section of gallbladder wall showing chronic state with superimposition of inflammation, edema and necrosis due to an acute episode.



A unique view of the gallbladder, from the inside looking out, by means of a true-to-life plastic model.



Cholecystitis from the pathogen's point of view

Vibramycin (doxycycline) penetrates gallbladder tissue to reach susceptible[1] pathogens

Vibramycin can be useful in cholecystitis because it provides a wide antibacterial spectrum and therapeutic tissue concentrations.[2] Vibramycin is active against susceptible[1] strains of bacteria including Escherichia coli and Enterobacter aerogenes (formerly Aerobacter aerogenes).

Concentrations of oral Vibramycin in gallbladder tissue removed from four surgical patients on a dosage of 200 mg. P.O. stat and 100 mg. P.O. once daily until surgery.[2]

Patient No.	Concentration in Tissue (mcg./Gm.)
1	5.80[3]
2	1.58
3	8.68
4	7.73

---

[1] Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

[2] Fabre, J. et al.: Schweiz. Med. Wochenschr. 97:915, May 17, 1967.

[3] Concentration in the bile taken simultaneously: 24.2 mcg./ml.

Vibramycin® I.V.

(doxycycline hyclate for injection)

100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.

200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

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See Brief Summary on following page for information on side effects and contraindications.

Penetrates tissue to reach susceptible* pathogens...

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100-mg. vials containing doxycycline hyclate equivalent to 100 mg. doxycycline with 480 mg. ascorbic acid.
200-mg. vials containing doxycycline hyclate equivalent to 200 mg. doxycycline with 960 mg. ascorbic acid.

Important facts about Vibramycin (doxycycline)

- can maintain therapeutic blood levels with a single daily infusion
- can be used without complexities of dosage alteration in patients with impaired renal function
- does not significantly elevate BUN in patients with renal insufficiency
- virtually the same broad range of indications when switching from I.V. to oral form

*Because not all strains of pathogens are susceptible, it is recommended that routine culture and susceptibility tests be performed.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated. Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

More detailed professional information available on request.

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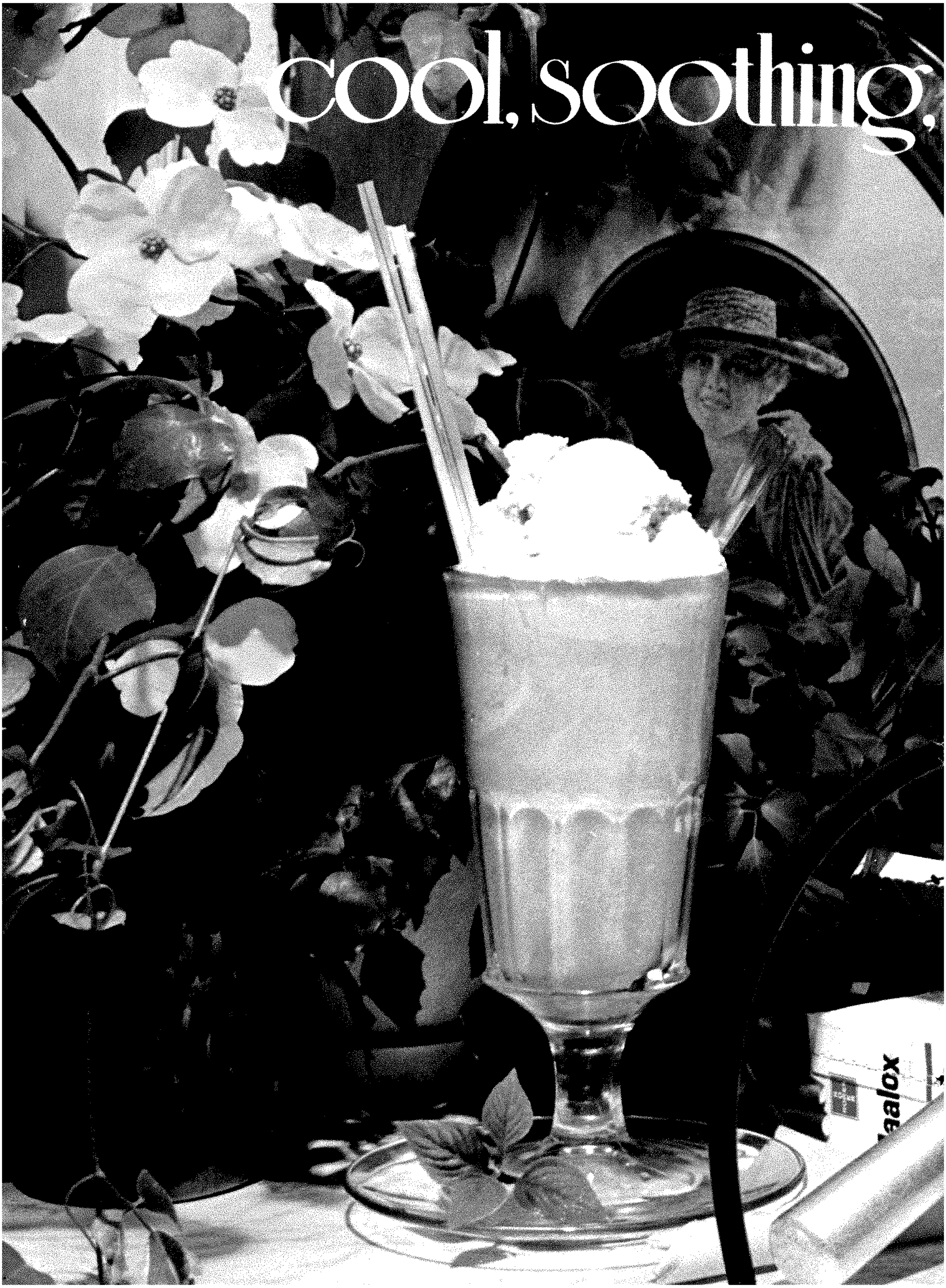

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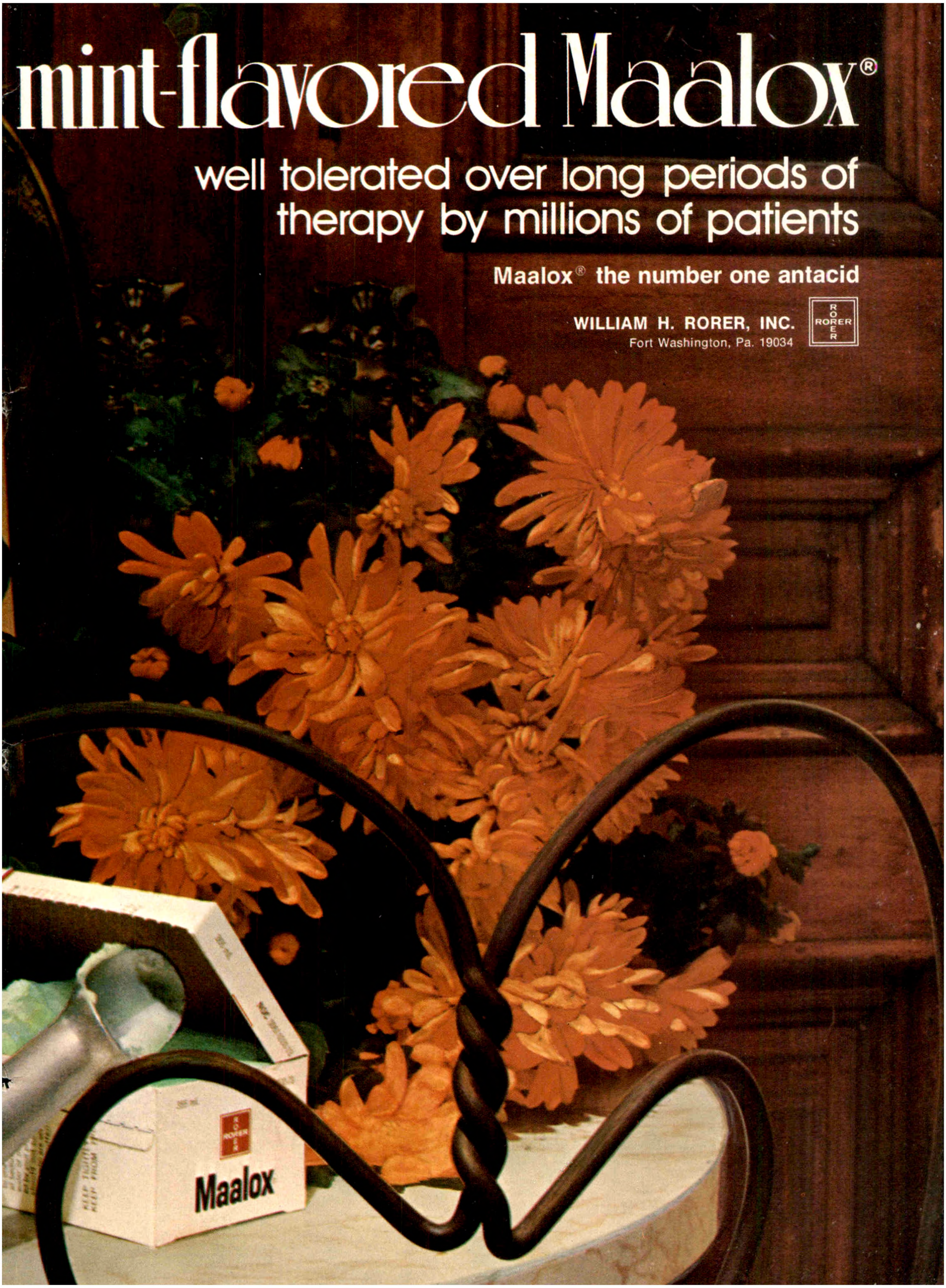

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Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

Administration and Dosage: A narcotic prescription is not required.

Darvon Compound-65 is given orally. The usual dosage is 1 Pulvule® every four hours as needed for pain. Each Pulvule contains 65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine.

How Supplied: Pulvules Darvon® Compound-65 (propoxyphene hydrochloride, aspirin, phenacetin, and caffeine, Lilly), in bottles of 500, in Identi-Dose® (unit dose medication, Lilly) in boxes of 100, and in Rx Paks (prescription packages, Lilly) in bottles of 100, in 25 packages of 30, and in 20 packages of 50.

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Indication: These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychosis and convulsions.

Administration and Dosage: A narcotic prescription is not required.

These products are given orally. The usual dose is 100 mg. propoxyphene napsylate and 650 mg. acetaminophen every four hours as needed for pain.

Drug Interactions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

How Supplied: Tablets Darvocet-N® and Darvocet-N® 100 (propoxyphene napsylate with acetaminophen, Lilly), in an Rx Pak (prescription package, Lilly) in 20 packages of 50, in bottles of 100 (Rx Pak) and 500, and in Identi-Dose® (unit dose medication, Lilly) in boxes of 100. Darvocet-N 100 is also available in an Rx Pak in 25 packages of 30. [102373]

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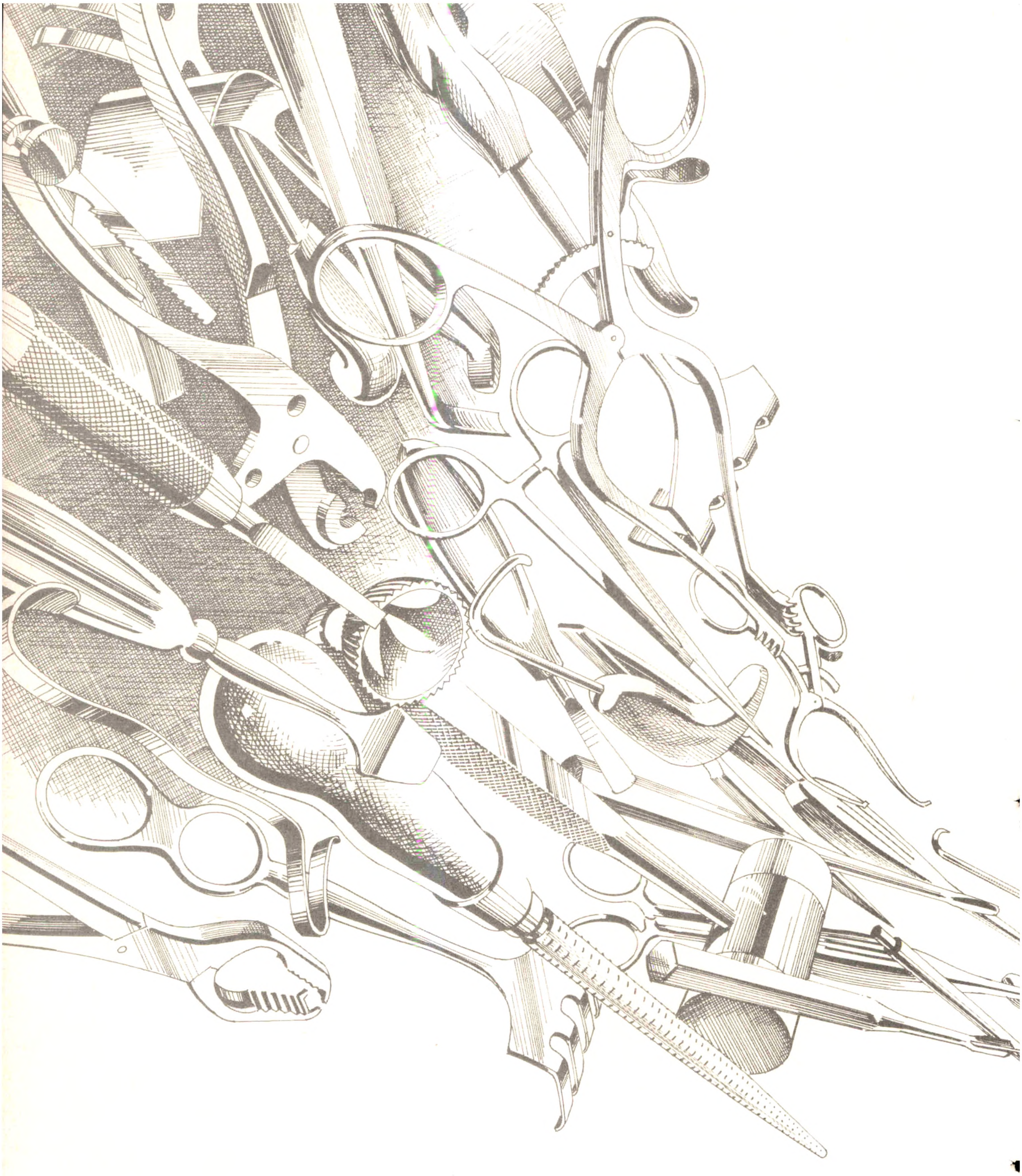

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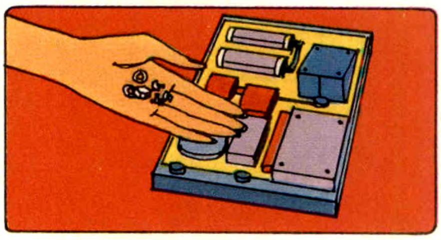

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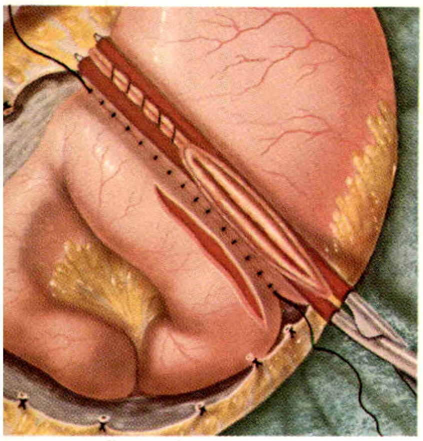
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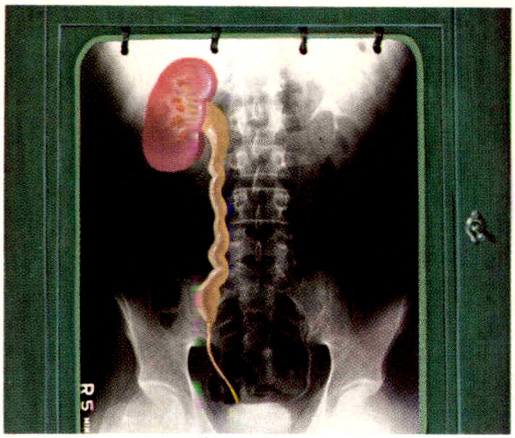

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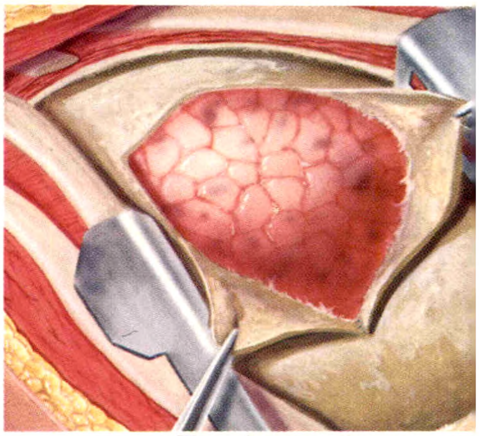
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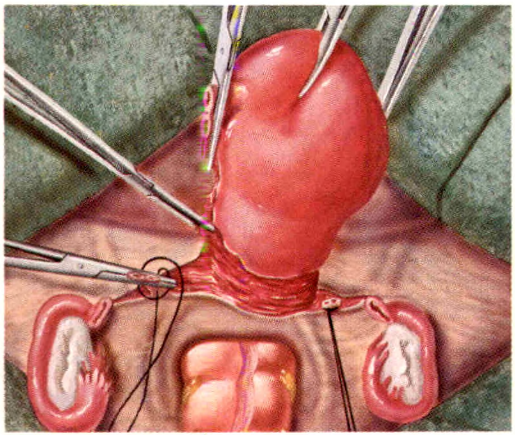
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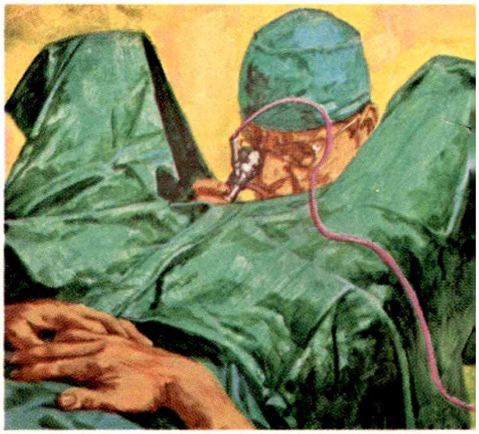
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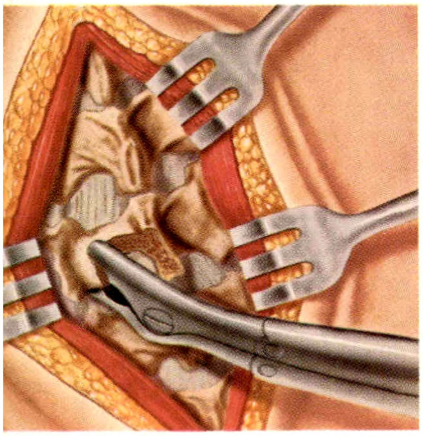
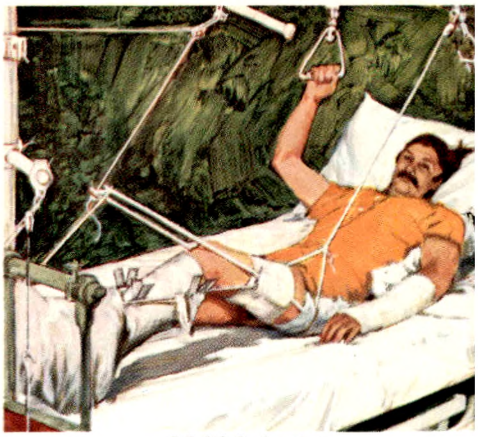
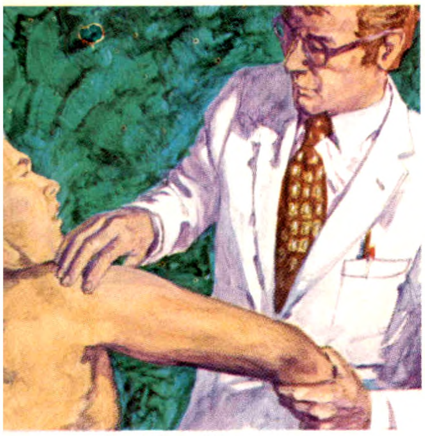
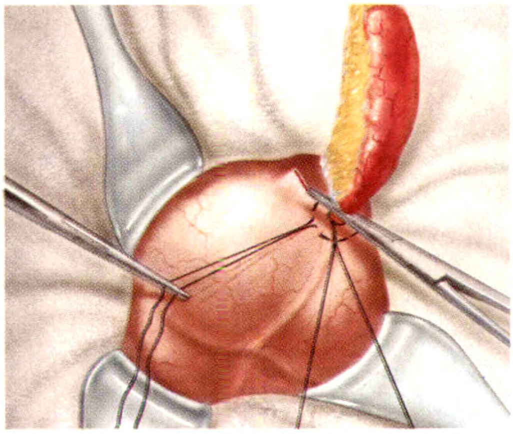
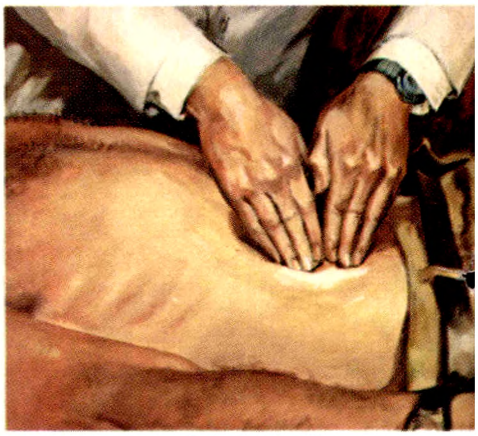

Laminectomy

Burns


Multiple fractures


Acute bursitis


Appendectomy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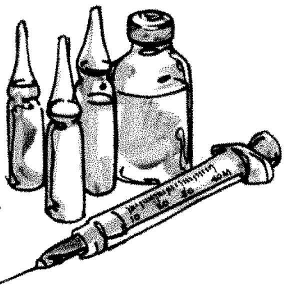

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Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

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Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

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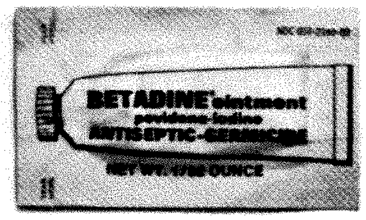

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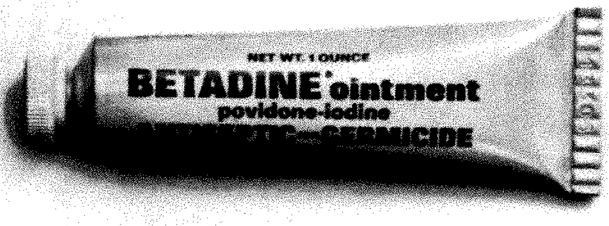

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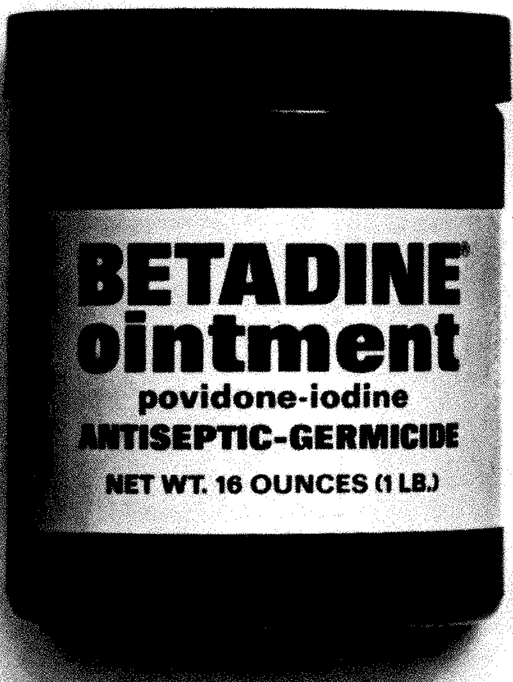

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Correction of Transposition of the Great Arteries:

Relationship of the Coronary Sinus and Postoperative Arrhythmias

P. A. EBERT, W. A. GAY, JR., M. A. ENGLE

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Between 1967 and 1973, 86 patients underwent total correction of transposition of the great arteries. There were 6 hospital deaths for an in-hospital survival of 93% with three late deaths. Seventy-two patients had repair with standard cardiopulmonary bypass and 14 infants were corrected with profound hypothermia and circulatory arrest. The incidence of postoperative dysrhythmia was less in the group in whom the coronary sinus was not incised but yet placed into the systemic venous return. Postoperative rhythm disturbance was greatest when the coronary sinus was widely opened and placed with the venous return. This observed decrease in incidence of atrial dysrhythmia may be related to not incising the coronary sinus and placing the sutures very superficial in the area between the sinus and the tricuspid valve.

In 1963, Mustard[10] performed the first intra-atrial baffle procedure to accomplish physiologic correction of transposition of the great arteries. Prior to this, only palliative procedures had been applicable although others had attempted total correction. Since that time, the operation has proved to be an excellent method of redirecting blood flow at the atrial level and accomplishing a physiologic result which allows the majority of these patients to enjoy near normal activities. There has been discussion regarding the proper technique for adjusting the tension on the intra-atrial baffle as well as the ideal material, whether it be autogenous pericardium or synthetic, to reconstruct the interior of the atrium.[5,8] Early and late postoperative arrhythmias have been troublesome with atrial tachycardia, flutter, or atrio-ventricular dissociation the most commonly observed disturbances. Several techniques for placement of the intra-atrial baffle and its position around the area of the coronary sinus have been suggested to reduce the incidents of rhythm disturbance.[1,2,8] This report summarizes our six-year experience with the intra-atrial baffle procedure for correction of transposition of the great arteries and relates the incidence of rhythm disturbance to the operative technique used in managing the placement of the baffle about the area of the coronary sinus.

Methods and Materials

During the six-year period, 1967 through 1973, 86 patients underwent intra-atrial baffle procedure for total correction of transposition of the great arteries. Twenty-six of these patients had a previous atrial septectomy performed either by the technique of Blalock-Hanlon or by open resection using inflow occlusion. At the time of total correction, the patients ranged in age from three weeks to twenty years (Table 1). Fifty-four of these patients had D-transposition of the great arteries with an intact ventricular septum or, at most, a very small ventricular septal defect and normal left ventricular pressure. Thirteen patients had ventricular septal defects of significant size which were closed during the time of total repair. Fourteen patients had a ventricular septal defect and associated pulmonary stenosis. In six of these, the stenosis was located at the pulmonary valve while, in eight, a subvalvular component was also present (Table 2). Six patients had previous pulmonary artery banding procedures for increased pulmonary flow. Two patients had a previous superior vena cava to right pulmonary artery anastomosis which was left undisturbed

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Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

TABLE 1. *Age at Time of Total Correction Transposition of the Great Arteries with the Method of Managing the Coronary Sinus*

	Months			Years			
	0–3	3–6	6–1	1–3	3–6	6↑	
Coronary Sinus Incised			1	14	4	2	21
Coronary Sinus Systemic		1	2	11	2	4	20
Coronary Sinus Venous	4	12	4	18	5	2	45
							86

TABLE 2. *Associated Anomalies Requiring Correction at Time of Intra-atrial Baffle Procedure*

	VSD	PS	VSD +PS	Uncom.	Total
Coronary Sinus Incised	3	1	3	14	21
Coronary Sinus Systemic	3		4	13	20
Coronary Sinus Venous	7	1	7	27	42
	13	2	14	54	86

at the time of intra-atrial correction. In four patients, a systemic to pulmonary shunt had been accomplished to increase pulmonary flow in infancy.

In 82 of the 86 patients, pericardium was used for the intra-atrial baffle. In four patients, either Teflon or Dacron was used because the pericardium was inadequate or damaged from previous operation. In 76 of the 86 patients a patch of pericardium or Teflon was used to enlarge the new systemic atrium. A vertical atriotomy was utilized which extended between the right pulmonary veins and across the inter-atrial groove.

The placement of the baffle in the area of the coronary sinus was managed in three ways:

1. In the initial 21 patients, the coronary sinus was incised posteriorly and the edges oversewn and operative repair accomplished very similar to the original technique described by Mustard[10] (Fig. 1).
2. In the subsequent 20 patients, the coronary sinus was not incised and the suture line of the baffle was placed so that the coronary sinus drained into the new systemic atrium (Fig. 2).
3. In the subsequent 45 patients, the coronary sinus was not incised but was placed with the unoxygenated venous return with the suture line positioned near the atrio-ventricular ring thus widely skirting the coronary sinus (Fig. 3).

The majority of the patients were maintained on ventilatory support for the initial 16–24 hours after surgery.

Results

There were six deaths occurring within 30 days of surgery for a hospital survival of 93%. There did not seem to be any correlation between the location of the coronary sinus and mortality except in one patient in which the coronary sinus was left with the oxygenated pulmonary return in which the baffle was too tight and inferior vena caval obstruction resulted.

The postoperative rhythm related to the position of the coronary sinus is shown in Table 3. Forty-nine of the

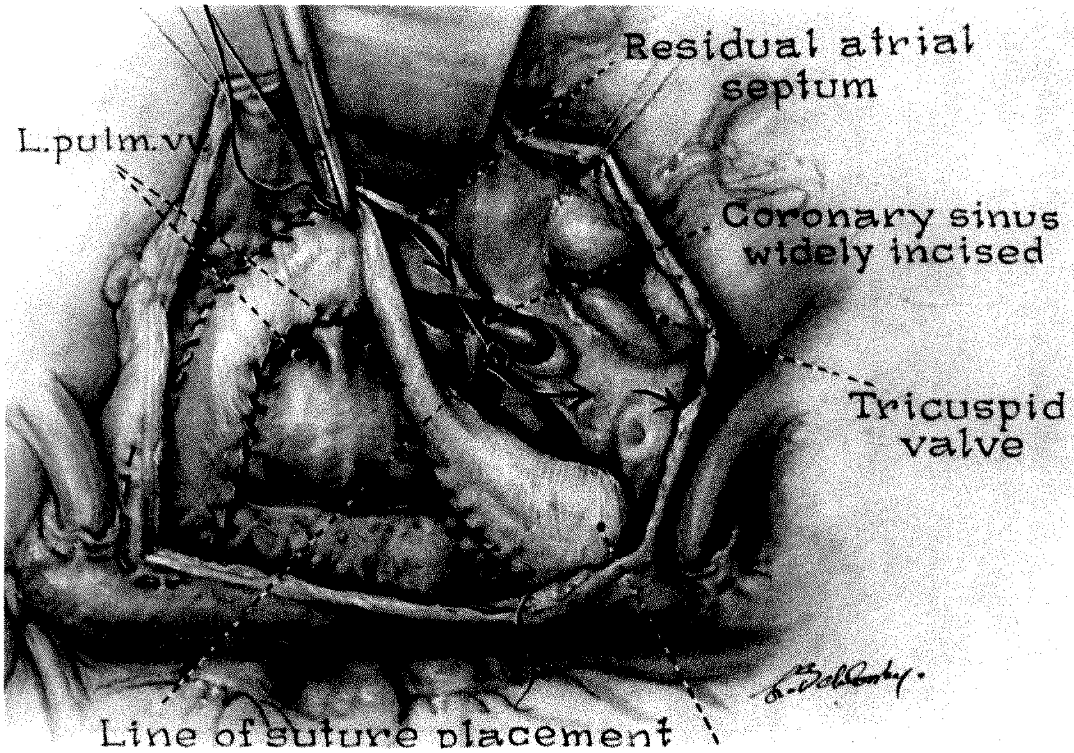

FIG. 1. Intra-atrial baffle shown partially sutured in position with the coronary sinus widely opened and the suture line extending inside the sinus to try to avoid the area of the atrioventricular node.

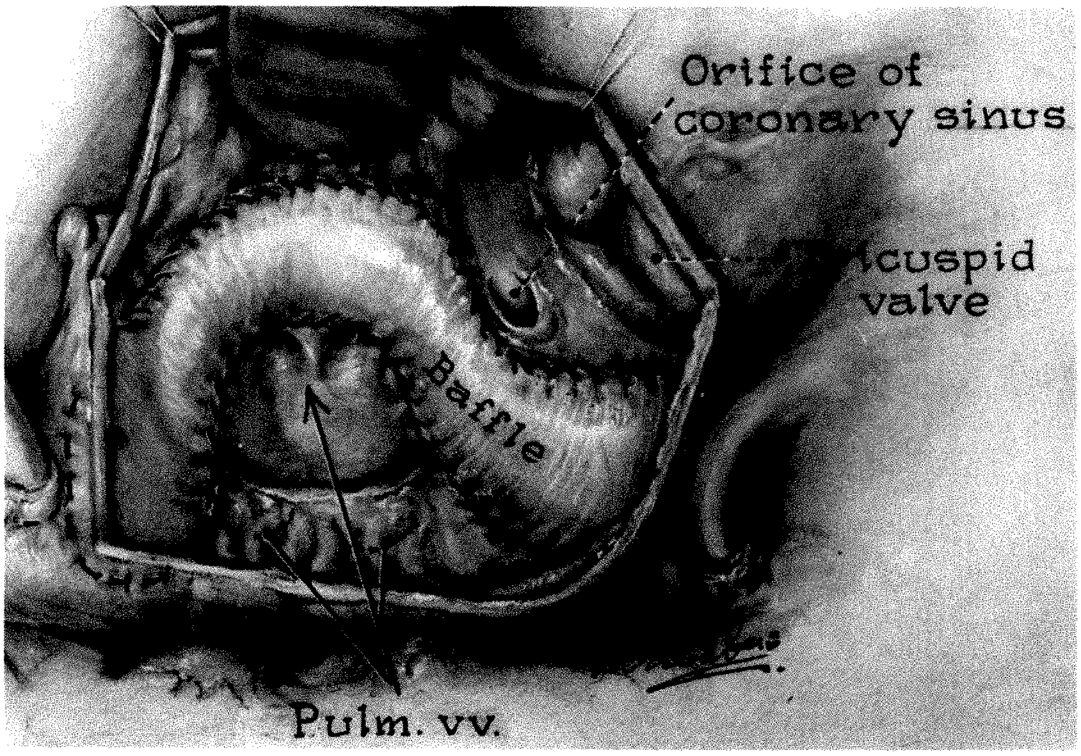

FIG. 2. The intra-atrial baffle is shown with the suture line going below the orifice of the coronary sinus. The sinus was not incised and now drains into the new systemic atrium receiving pulmonary venous return.

86 patients are thought to be in sinus rhythm with an additional 24 in atrial rhythm. It is difficult to define clearly sinus rhythm from an atrial rhythm where the atrial impulse originates in a position other than the sinus node. Two patients in each group had atrio-ventricular dissociation with a junctional type rhythm. Heart rates ranged at rest from 74 to 86. None of these patients required the use of a pacemaker. Seven patients have had periodic episodes of atrial flutter. When the coronary sinus was incised, as in the original technique, six of these 21 patients have been documented to have atrial flutter with periods of a rapid ventricular response. In three of these patients the episodes with atrial flutter have been able to be controlled by Digitalis and with increasing age, the episodes seem to have subsided. Two late sudden deaths were possibly related to an episode of atrial flutter. One patient had frequent episodes of atrial flutter which were uncontrolled by any type of medication and he underwent elective exploration of the atrium to incise the area about the AV node in an attempt to produce atrioventricular dissociation. This was unsuccessful and the patient expired. Only one other patient among 65 had been known to have repetitious episodes of atrial flutter and these have been reasonably controlled with digitalis. Eight others have had early episodes of atrial tachycardias of ectopic origin but have been easily controlled with digitalis. In acute episodes of atrial flutter, with a 2 to 1 ventricular response, heart failure and severe symptoms have been managed by electro-conversion. No particular drug or combinations of drugs have been uniformly successful in controlling or reversing these episodes of atrial flutter with rapid ventricular response.

In 72 of the patients, standard cardiopulmonary bypass with 50% hemodilution and moderate hypothermia was used during the operative repair. In 14 infants profound hypothermia with surface cooling to 25C followed by extracorporeal circulation for core cooling to 14C and later rewarming was utilized. The 6 hospital deaths occurred in patients undergoing correction with standard cardiopulmonary bypass. These 6 hospital deaths are listed in Table 4. There was no one consistent cause of death and the two technical problems were related to incomplete relief of subvalvular pulmonary stenosis in one patient and the atrial baffle being positioned too tight about the area of the inferior vena cava when the coronary sinus remained with the pulmonary venous return. Five additional patients are known to have obstruction of the superior vena cava as documented by cardiac catheterization. Three patients have been totally asymptomatic and the finding was an incidental one at the time of re-study. One patient developed modest swelling of the arms and head which subsided after four weeks. An additional patient presented three months after operation with symptoms of profound respiratory insufficiency and congested lung fields. The initial diagnosis was obstruction of the pulmonary venous return but at the time of re-operation this was found to be normal and the superior vena cava obstructed. Relief of the superior caval obstruction relieved the pulmonary congestion which sub-

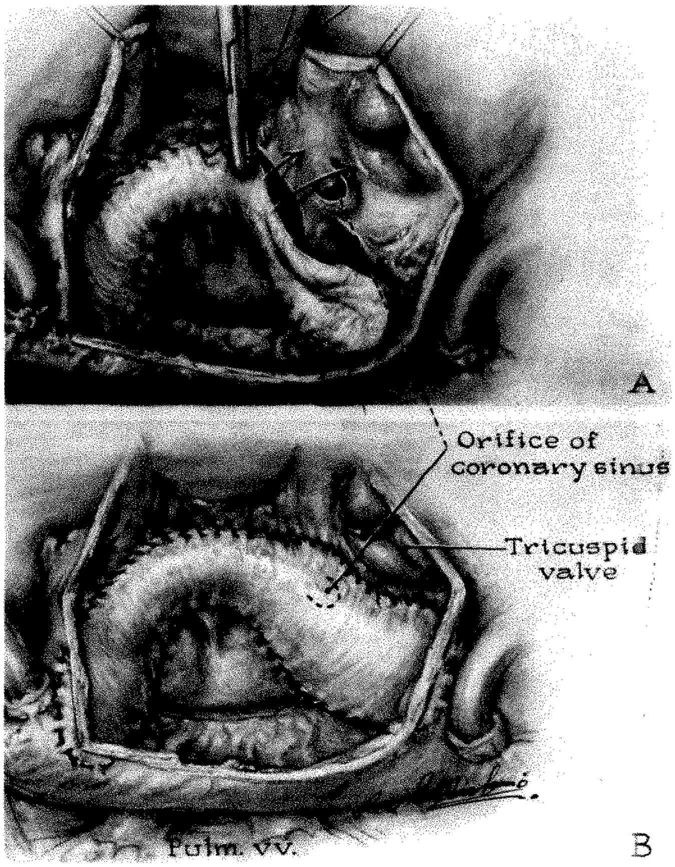

FIG. 3. "A" shows the relationship of the intra-atrial baffle to the coronary sinus, noting that the sinus has not been incised but will be positioned with the systemic venous return. In "B" the baffle is sutured to the rim of atrial septum with care being taken not to attach it directly to the tricuspid valve. The position of the coronary sinus is identified.

TABLE 3. *Postoperative Rhythm Related to Management of the Coronary Sinus at Operative Correction*

	Normal Sinus Rhythm	Atrial Ryhthm	Atrio-Ventricular Dissoc.	Atrial Flutter
Cor. Sinus Incised-21	7	6	2	6
Cor. Sinus Systemic-20	13	4	2	1
Cor. Sinus Venous-45	29	14	2	0
	49	24	6	7

sequently was thought to be lymphatic stasis due to the high superior vena cava pressure.

Pulmonary venous obstruction was not documented in any patients. This was thought to be related to placement of a patch in the systemic atrium in 76 of the 86 repairs. Only 10 patients did not have their systemic atrium enlarged and these were generally older patients who had a previous Blalock-Hanlon operation and the two patients who had previous superior vena cava to right pulmonary artery anastomosis.

In three patients, moderate tricuspid insufficiency was present before surgery and in one tricuspid insufficiency was severe due to injury of the tricuspid valve with balloon septostomy. In this patient, repair of the tricuspid valve at the time of operation, has corrected the tricuspid insufficiency. A partial annuloplasty was performed in an additional patient with some improvement in tricuspid insufficiency. The remaining two patients have done well since the intra-atrial baffle procedure but still have a murmur of mild tricuspid insufficiency. Twenty-seven patients had ventricular septal defects. In four, the defect was reasonably small and was not closed at the time of operation. In 20 of the 23 closed, the repair was accomplished through the atrium with retraction or detachment of the tricuspid leaflet. In two, the defect was quite large and was closed through a ventriculotomy in the systemic right ventricle. In one patient, the defect was closed through the pulmonary artery.

Discussion

Operative repair for transposition of the great arteries has had a high degree of success and is being performed in very young infants with optimistic results.[3,7,12] These results in infants with total correction as compared to palliative operations have been extremely encouraging as ablation of the right to left shunt obviates serious complications such as systemic emboli, brain abscess, etc. The common complications contributed to total correction have been heart failure, pulmonary venous obstruction, and rhythm disturbances. The lack of significant pulmonary complications in this series of cases may be related to the routine enlargement of the systemic atrium so that obstruction of pulmonary veins would be an uncommon observation.[4] This routine enlargement of the systemic atrium allows the baffle to be placed more loosely and should decrease the incidence of caval obstruction. In the four patients with caval obstruction, two had pericardium used for the baffle and two had a prosthetic material. We have had minimal experience with prosthetic materials and have felt that the marked degree of stiffness caused by infiltration with fibrous tissue would make these a less desirable choice for such a large curving structure needed for the intra-atrial baffle.

It is difficult to correlate whether the association of a decrease in rhythm disturbance with alteration in the operative technique in the area of the coronary sinus is

TABLE 4. *Causes of Death in Six Patients who Expired Within Thirty Days of Operative Repair*

1. 3 yr. VSD, PS—Respiratory Insufficiency—Large Bronchial Flow
2. VSD, PS—Incomplete Relief of PS
3. Atrial Baffle Too Tight—Restrict Venous Return
4. Transfusion Reaction—Bleeding
5. VSD—Severe Pulmonary Hypertension
6. Aspiration Pneumonia

directly related or whether this is simply an expected improvement as more experience in operative repair is gained. However, placement of a very superficial suture line at some distance to where the atrio-ventricular node is thought to be located may be of benefit. This suture line has not been placed in the tricuspid or mitral valves as suggested[2,8] but has been placed superficially in the right side of the remnant of the atrial septum. The possibility of fibrous ingrowth damaging valve function seems likely and the complication of either tricuspid or mitral insufficiency occurring in even a small percent of patients seems unnecessary. However, the most distressing arrhythmia in the transposition has been that of atrial flutter which may be related more to the numerous incisions and suture lines placed in the atrium. Enlargement of the coronary sinus may be unnecessary and is an additional atrial incision which could be related to the occurrence of atrial flutter or atrial dysrhythmias such as the so-called coronary sinus rhythm. Obviously, the sinus node can be damaged by placement of a catheter in the superior vena cava and attempts have been made to place the purse string on the lateral side of the superior vena cava as far away as possible from the area of the sinus node.

The actual incidence of arrhythmia in the present series was 40% if one counts the 24 patients with an atrial rhythm in whom the impulse originates in other than the sinus nodes. But only 18% of these patients had atrial flutter or atrio-ventricular dissociation which would be considered serious dysrhythmias. This is not too dissimilar from other reports.[5,6,9,13] In the early postoperative period the occurrence of atrial flutter is best treated by immediate electroconversion. In our experience, attempts at management by any pharmacologic methods have, in general, been unsuccessful. Reversion of atrial flutter in each of the 7 patients observed to have this dysrhythmia in the hospital was accomplished by cardioversion. In general, a patient having sign of rhythm disturbance has been maintained on digitalis for at least six months after operation. The seriousness of dysrhythmias are often overlooked since the patient hemodynamically is quite stable but may be susceptible to sudden death months to years after the time of corrective surgery.

The success of correction in infancy, using profound hypothermia, has changed the approach to patients with transposition of the great arteries. As previously mentioned, most all infants with transposition of the great arteries should have balloon septostomy.[6,11] If the infant does not show dramatic improvement following this, elective correction with profound hypothermia and circulatory arrest appears indicated. Obviously, the associated lesion of pulmonary stenosis is more difficult to correct in a small infant and a palliative procedure may be indicated in some severe forms of pulmonary stenosis. Ventricular septal defect seems adequately managed in the infant by direct closure. Changing spectrums and advances in care of this annomaly make it difficult to present a standardized approach to the disease, but the hospital survival of 93% and a current long-term survival of 90% in this series seems most optimistic. It is certainly possible that as the infant or young child grows, revision of the baffle may be necessary as it may not be possible to accomplish a lasting correction when the baffle is placed at such a young age. However, only long-term results with periodic evaluations will answer this question.

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Discussion

Dr. Eoin Aberdeen (Philadelphia): Drs. Ebert, Gay and Engle and their Cornell team are to be very warmly congratulated on the results they have just reported. I would emphasize that not only have they reported a 93% survival for transposition surgery, which most people would be happy to accept for straightforward transpositions, but they have included their complex cases as well, and I believe these results are as good as anyone else has produced.

It may be impertinent to suggest any alterations in their management, because their results are so good, but I believe that their second method of management has some advantages to it, judged by the experience of others.

(Slide) At the Hospital for Sick Children in London we performed the first 55 Mustard operations from 1965 to 1967, and found a high incidence of arryhthmias afterwards, especially the one that Dr. Ebert fears most, atrial flutter, which can be associated with sudden death two to three years after operation.

We reviewed the conduction problems, and decided that the two most important things were to keep away from the sinus node firstly, because most atrial flutters originated, I believe, from damage to the sinus node; and secondly, the problem that cardiac surgeons have faced for so long now, to avoid any damage to the conduction system from the AV node downward.

It therefore seemed to us reasonable not only to avoid, by as big a distance as possible, the sinus and the AV nodes, but we also gave consideration to what was known of the internodal conduction pathways, the anterior, the middle, and the posterior, recognizing that the middle pathway must be destroyed when the atrial septum is removed to do the Mustard operation.

So we proceeded, then, having got 14 atrial flutters in our first 55 cases, to place a patch that avoided, where possible, the posterior internodal pathway and the anterior, and found that in the next 100 cases there were only three episodes, briefly, of atrial flutter, and none were persistent.

So we seemed to have got around the atrial flutter problem, but there were still some AV dissociations. But the arrhythmia problem, by carefully avoiding both nodes, was certainly vastly less than it had been in the earlier part of the series.

I think we made an error in thinking it so important to avoid the posterior internodal pathway. I now would accept what many others have done, to put the patch across the crista terminalis to get a bigger IVC flow path and to include the eight atrial appendages in the new systemic atrium, rather than in the pulmonary atrium.

The other point we did was to retain some of the atrial septum to help route the IVC flow. In the next hundred cases we used some Dacron, believing this would make it less likely that the patch would shrink. We now have evidence that this is not an advantage, and now prefer to perform the operation entirely with pericardium, and preserving this portion of the atrial septum here (indicating) to help route the IVC pathway.

There was one other factor. It was a single case, but it was one of those that influences one, inasmuch as a child who had been two years following a successful Mustard operation (slide) developed a heart block, and finally died three years postoperation, and we found at postmortem that here is the conduction bundle, here is the suture, and here is a large lump of cartilaginous tissue that had grown into the bundle and blocked it.

We therefore felt that we wanted to get all our suturing away from the bundle as much as possible. Now, I recognize that this is only a single case, and the experience with ostium primum repair would suggest this is not a common problem. But, nevertheless, we'd still prefer to get our suture line entirely away from the AV node and the AV bundle, if possible.

Finally, an assurance about the late results, (slide) recently the first 19 cases we did of Mustard's operation in children under one year of age between 1967 and 1970 have been reviewed at Great Ormond Street, and it was found that, of the 17 survivors, one had a late pulmonary venous obstruction—a child operated on at three months—but there have been no caval obstructions. The children are very well. They are pink. The fact that the coronary sinus is draining into the pulmonary venous atrium has not affected their saturations, and there is evidence that the pericardial partition has grown.

So I think the long-term outlook—long-term in the intermediate sense of the next 10 or 20 years, at least—is good. We don't need to worry too much, about IVC obstruction, using atrial septum and pericardium, although we do need to worry about it using Dacron in the small children—that is, in children of three to nine months of age.

The experience of Dr. McGoon and the Mayo group, using a Dacron partition in the slightly older children, has been so good that it's clear we don't need to worry about it in the older ages; but, I think, there are advantages in using pericardium in those being operated on between three and nine months of age.

It is a conclusion of interest that not only have we found operating on infants under a year with this operation to be as good as the results in our children over a year; it has been considerably better in many hands, and this lends support to two views: 1) the infant is not a very fragile surgical specimen; the infant is a tough surgical specimen; and 2) since most of these cases have been operated on with cardiopulmonary bypass, cardiopulmonary bypass, in fact, can be a very safe medium in handling major heart surgery in infants. (In the first weeks of life I prefer to use the hypothermic arrest technique).

Dr. Bruce C. Paton (Denver): I'd like to reemphasize the point about the use of Dacron in infants under one. We have used Dacron in eleven infants under one, and have had to reoperate on two of them for pulmonary venous obstruction, both successfully. The opening seen at the second operation was about as big as a pencil, and the Dacron had contracted down into a round, circular ring. In both cases the posterior atrium was enlarged with a pericardial patch extending down between the right pulmonary veins. [Applause]

Dr. Paul A. Ebert (Closing discussion): I think the illustration Dr. Aberdeen showed is probably the most important point; that is, that preservation of atrial tissue is probably more significant than was initially given credit. I think we have all adopted a more delicate suture technique; and whether one puts the baffle below or above the coronary sinus probably is not terribly critical. I think either can accomplish the same result, as far as avoidance of dysrhythmia is concerned. But if one puts extremely deep bites, or excises back across the middle pathway, then I think we're probably going to be faced with more problems with atrial flutter.

I'm a little concerned that we haven't seen the final chapter of this disease yet, and I am concerned that more children may come back at a later time with yet unrecognized problems.

I appreciate Dr. Paton emphasizing the problem with Dacron. We have had little experience with it. We have had two children in whom Dacron was put in at an older age where the Dacron had actually grown to the opposite wall and whom we have reoperatived on for relief of their superior vena caval obstruction.

The Long-term Influence of Coronary Bypass Grafts on Myocardial Infarction and Survival

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Approximately 1,000 coronary bypass procedures were performed at New York University between February 1968 and December 1973. This report reviews all elective operations performed for angina between 1968 and 1972, a total of 448 patients. In this five-year period the percentage of diseased arteries bypassed rose from 40% to 84%, and operative mortality decreased from 28% to less than 3%. There were a total of 28 operative deaths, mostly from myocardial infarction and low cardiac output. Operability was nearly 95%. The only fixed contraindication was chronic congestive failure. Over one-half of the patients had an abnormal ventriculogram, and there was some history of mild congestive failure in nearly 20%. Elevation of left ventricular end-diastolic pressure above 20 mm before operation was associated with a higher operative mortality, but the late mortality was similar to those with a normal preoperative end-diastolic pressure. In 383 surviving patients, angina was eliminated or greatly improved in 86%, unimproved in 12% and worse in 2%. Late angiograms were performed on 201 patients, studying a total of 445 venous grafts with an overall patency rate of 71%. Graft occlusion was sporadic and unpredictable, but over 90% of patients with multiple grafts remained with at least one patent graft. A late myocardial infarction occurred in 32 out of 420 patients surviving operation, and was fatal in eight. The cumulative incidence over a period of five years was 17%. Twenty-three deaths occurred following discharge from the hospital. Life-table analyses showed a five-year survival of 77% when all deaths were included, and a five-year cardiac survival of 81% when non-cardiac deaths were withdrawn alive at the time of death. The expected survival in a comparable population group without coronary disease was 92%, while data published by Sones of patients treated without operation showed a five-year cardiac survival of 66%. Current operative techniques have an operative mortality of 2–3% and a subclinical infarction rate of 5–10%. The ideal graft is yet evolving, but data with internal mammary artery grafts are most encouraging. A future goal should be a five-year graft patency of at least 80%. Because many infarcts probably develop from a relatively small decrease in coronary blood flow, either during rest or mild activity, the likelihood that future data will demonstrate a marked increase in longevity with bypass grafting is great.

THE FIRST CORONARY BYPASS operation was done at New York University in February 1968, an anastomosis of the internal mammary artery to the left anterior descending coronary. During 1968 and 1969 the procedure was cautiously applied to selected patients, but with the prompt relief of angina in most patients, the number of operations rapidly escalated to create the serious logistical question about how many bypass operations could be done annually with the institutional resources available. The decision was made to perform no more than 200–300 operations each year. This limit has been followed since 1970. Hence, the patients operated upon have been automatically selected to some degree as those most seriously disabled with angina, while those with lesser disability were either advised to be operated upon at another hospital, or else operation was not recommended.

By the end of 1973, over 1,000 bypass operations had been performed. For this analysis of late results, only the *elective* bypass operations for angina were considered from the first operation in February 1968 through December 1972, a total of 448 patients. Emergency procedures, operations for pre-infarction angina or myocardial infarction, and those combined with excision of ventricular scars and aneurysms or insertion of prosthetic valves, were excluded.

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* By invitation.

Methods

Indications for Operation

Operation was usually recommended for angina incapacitating the patient from normal activity despite the best medical therapy possible. This of course was a subjective decision influenced by the age, vocation and personality of the patient, as well as the experience of the referring physician. Operation was not advised on a prophylactic basis for angina controlled with medication or for the angiographic demonstration of occlusive disease in an asymptomatic patient. A prophylactic bypass was done only for the unusual condition of occlusive disease in the left main coronary artery, constituting less than 10% of operations performed.

Contraindications to Operation

Within the above criteria, an aggressive policy was pursued to evaluate the applicability and limitations of bypass. Virtually no fixed contraindications to operation were found except protracted congestive heart failure. Advanced age, diabetes, and hypertension were common but were not considered major contraindications. A large percentage of patients had varying degrees of injury of the left ventricle revealed on the ventriculogram, with elevation of end-diastolic pressure (Tables 2, 3), but unless chronic congestive failure was present, operation was recommended. With this aggressive policy, nearly 95% of patients considered candidates for operation were operated upon.[9]

Preoperative Evaluation

The two basic studies before operation were angiography and ventriculography. Significant obstruction was considered present on the angiogram when the diameter of the artery was narrowed more than 60–70%, representing a decrease in cross-sectional area greater than 75–80%. Neither the ability to opacify the artery beyond the obstruction, nor the size of the distal artery were consistently used as a criterion for operation. The ideal angiographic candidate, of course, was one in whom a 2 mm artery could be seen distally. However, a significant number of patients were operated upon in whom no major artery could be seen beyond the obstruction or the artery distally seemed small, near 1 mm, but was found at operation to be 2 mm or larger. This varying ability to opacify arteries distal to an obstruction probably reflected the variation in amount of collateral circulation present. The only angiographic contraindication to operation was an artery with multiple areas of diffuse obstruction throughout its course. Fortunately this was rare.

Ventriculography was used to estimate the degree of injury of the left ventricle; a subjective decision based upon the extent of impaired contractility from previous infarction and fibrosis. Left ventricular end-diastolic pressure was also measured. More complicated methods of estimating left ventricular function, such as ejection fraction, were not used.

Operative Technique

Details of the operative technique have been described previously;[10] only certain points will be emphasized here. A standard cardiopulmonary bypass was used, with a Temptrol bubble oxygenator and DeBakey roller pumps. Pump prime was a non-blood balanced electrolyte solution, virtually identical to plasma, with 25 g/L of albumin. Perfusion was at a flow rate near 3L/m^2/min, at 25–30 C. During perfusion mean blood pressure was kept *near that existing beforehand*, a technique employed regularly for the last three years and considered of particular importance in older patients with diffuse atherosclerosis and hypertension. Most anastomoses were performed during induced ventricular fibrillation. In recent years the heart has been periodically defibrillated during the procedure to permit monitoring of the electrocardiogram for any signs of ischemic injury. Periods of ischemia induced by clamping the aorta were progressively limited in extent, rarely using periods longer than 15 minutes and often avoiding clamping of the aorta altogether. A left ventricular vent was almost always used, with monitoring of the left atrial pressure. The duration of perfusion varied from one to more than four hours.

Before bypass was started, a segment of saphenous vein was removed from the lower thigh or upper leg and kept in a 4 C Plasmalyte solution. For the past two years the left internal mammary artery has been regularly used, with the most common procedure being a triple bypass with anastomosis of the left internal mammary artery to the anterior descending coronary, and vein grafts to the circumflex and right coronary arteries. Vein grafts were used however for most operations described in this report. During operation, an attempt was made to bypass almost all diseased arteries, performing a double or a triple bypass in most patients.

Certain points of operative technique should be emphasized. Currently most anastomoses are done end-to-side with interrupted or continuous 6–0 or 7–0 Prolene sutures. Following completion of the distal end-to-side anastomosis with a vein graft, the vein was carefully attached to the surface of the epicardium with sutures about 5 cm apart to curve the vein in a sinusoidal course over the surface of the heart, permitting a free range of motion during cardiac contractions. Straight grafts were avoided. Grafts to the right coronary artery were brought up over the right ventricle, while those to the circumflex were curved along the left atrial-ventricular groove and then across the right ventricular outflow tract and up to the aorta. This avoided crossing the pulmonary artery. The aortic anastomoses were done with a simple 1 cm longitudinal aortotomy, performing an end-to-side anastomosis with continuous 6–0 Prolene. Meticulous care was taken to remove air from the vein grafts before flow of blood was started. Internal mammary artery anastomoses are currently done by dilating the artery with 30 mg of papaverine placed intraluminally beforehand, and then performing an end-to-side anastomosis with interrupted and continuous 7–0 Prolene sutures.

Following bypass, the rate of blood flow in each graft was measured with a flowmeter, finding a mean flow ranging from as small as 20–30 ml/min to as large as 60–80 ml per min. This, of course, varied primarily with the size of the artery grafted. Before closing the incision, the vein grafts were carefully covered with pericardium in the latter part of the series, as earlier observations indicated that adhesions were much more severe when mediastinal fat, rather than pericardium, was placed over the vein grafts.

Postoperative Care

The essentials of postoperative care were based upon continuous monitoring of the electrocardiogram and the O_2 and CO_2 concentrations in arterial and mixed venous blood. Blood samples were obtained through indwelling catheters left in a peripheral artery and the pulmonary artery at the time of operation. The basic objective was to maintain a PO_2 of 30 mm Hg or greater in the mixed venous blood, this level indicating an O_2 transport by the circulatory system which was adequate for body needs.[1] This method of postoperative monitoring has been regularly used for over 15 years. The most common causes of inadequate O_2 transport were cardiac failure, hypovolemia, or inadequate ventilation. Mechanical ventilation was usually done for a few hours following operation but seldom longer. Tracheostomy was rarely used. Infusions of blood and electrolyte solutions to adjust blood volume were monitored from left atrial or pulmonary artery diastolic pressure. If cardiac failure was present, small amounts of inotropic drugs, 1–2 mcg/min of isoproterenol or epinephrine, were given.

Anticoagulants were used following operation early in the series but not thereafter. Most patients were discharged from the hospital within nine to fourteen days after operation.

Late Management

Following discharge from the hospital, the patients returned under the care of their referring physician but were periodically seen in an out-patient cardiac clinic. As virtually all patients lived within the vicinity of New York City, followup examinations could be readily obtained. Repeat angiography six months following operation was routinely encouraged and accomplished in 201 of the 420 patients surviving operation (48%). In the summer and fall of 1973 a 96% followup of the 448 patients described in this report was accomplished by telephone or by questionnaire, seeing selected patients personally for an out-patient evaluation. Specific attention was given to the determination of the occurrence of angina, infarction, or death.

Statistical Methods

Survival and cumulative incidence curves were obtained by the product-limit life-table method of Kaplan and Meier.[12] When analyzing for the influence of bypass surgery on cardiac-related deaths, non-cardiac deaths were withdrawn alive at the time of death; similarly, when calculating the cumulative incidence of myocardial infarction for patients surviving operation, deaths not related to myocardial infarction were withdrawn alive at the time of death.

Results

Initial Results

The data for the five-year period (1968–1972) are tabulated in Table 1, showing the number of operations performed annually, the frequency of different types of bypass and the operative mortality. Two changes gradually occurred in the series, an increasing number of bypasses performed and a steady decrease in operative mortality. Before 1971 a triple bypass was seldom done because of lack of familiarity with the technique of grafting of the circumflex coronary, as well as the belief that a less extensive operation might be satisfactory.

TABLE 1. *Overall Experience*

				Operative Mortality	
Year	Total No. of Patients	Type of Surgery*	No. of Patients	No. of Operative Deaths	% Mortality
1968	14	SCB	11	2	28.6%
		DCB	3	2	
		TCB	—	—	
1969	31	SCB	6	0	6.5%
		DCB	22	2	
		TCB	3	0	
1970	73	SCB	12	0	10.9%
		DCB	58	8	
		TCB	3	0	
1971	152	SCB	23	0	6.5%
		DCB	59	6	
		TCB	70	4	
1972	178	SCB	21	0	2.2%
		DCB	63	1	
		TBC	94	3	

* SCB: single coronary bypass
DCB: double coronary bypass
TCB: triple coronary bypass

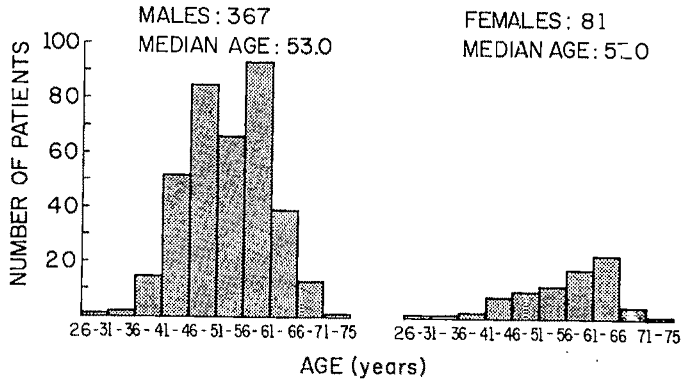

FIG. 1. Histograms of age by sex for 448 patients undergoing coronary bypass surgery between February 1968 and December 1972.

This policy was changed in 1971–1972 to where a triple bypass became the procedure most commonly performed, while a single bypass was rarely done. In the total of 448 patients, 170 had a triple bypass, 205 a double, and 73 a single.

A retrospective analysis of the number of bypass grafts inserted in comparison to the extent of arterial disease, single, double, or triple occlusive disease, was done for the entire period of five years. Between 1968 and 1970, the percentage of patients who had adequate grafts at operation gradually rose from 40 to 63%. During 1971 and 1972, with the increasing use of triple bypass, 84% of diseased arteries were grafted.

The operative mortality decreased from an initial high level of 28% in 1968 to 6% the following year. Since the end of 1971 it has remained less than 3%.

Patients ranged in age from 26 to 72 years (Fig. 1). Eighty-two per cent of the 448 patients were male, with a median age of 53, while 18% were female, median age 57.

Preoperative ventriculography found some impairment of ventricular function in approximately one-half of the patients (Table 2), while in 44% it was normal. There was a localized area of hypokinesis in 27%, a saccular aneurysm in 5%, and diffuse hypokinesia in 17%. Seven per cent of the patients had an inadequate ventriculogram. Corresponding with the frequency of impaired ventricular function was the finding that there was some history of congestive heart failure before operation, usually either mild or intermittent, in about one patient in five (19%). The principal symptom was dyspnea on exertion. On the other hand, about one patient in six (16%) with normal ventricular function had some symptoms, usually dyspnea, consistent with transient congestive failure.

TABLE 2. *Preoperative Left Ventriculogram in 448 Patients*

Description of LV	Number of Patients	%
Normal	199	44%
Diffuse Hypokinesia	76	17%
Local Hypokinesia	120	27%
Aneurysm	23	5%
Inadequate Ventriculogram	30	7%

TABLE 3. *Frequency of Late Death: Number of Grafts and Preoperative LVED*

No. of Grafts	LVED ≤ 12 No. of Patients	No. of Deaths	LVED 13–19 No. of Patients	No. of Deaths	LVED ≥ 20 No. of Patients	No. of Deaths
One	43	1	16	1	4	0
Two	100	3	49	5	18	0
Three	85	4	55	1	16	1
Totals	228	8	120	7	38	1
		(3.5%)		(5.1%)		(2.5%)

The left ventricular end-diastolic pressure was measured in 91% of patients and found elevated in 42% (Tables 3, 4). The relationship between end-diastolic pressure, the number of grafts inserted at surgery, and operative and late deaths is shown in Tables 3 and 4. Mild elevation of end-diastolic pressure (13–19 mm Hg) had no significant influence on operative mortality (2.4%) when compared with normal end-diastolic pressure (3.4%); but an end-diastolic pressure above 20 mm Hg was associated with a significantly greater mortality (22.4%) (Table 4). However, an elevated end-diastolic pressure before operation did not indicate a serious prognosis for those patients surviving operation (Table 3). The three-year survival for patients surviving operation was virtually identical for those with an elevated end-diastolic pressure as compared with those in whom it was normal, approximately 92%.

There were a total of 28 operative deaths in the overall series of 448 patients (Table 5). Most were due to either myocardial infarction or a low cardiac output. The incidence of subclinical infarction following operation was low, probably in the range of 6–10%. This incidence has been found in two consecutive series of patients studied.[4,18] Such infarcts usually produced no hemodynamic signs but were detected from either the electrocardio-

TABLE 4. *Operative Mortality: Number of Grafts and Preoperative LVED*

No. of Grafts	LVED ≤ 12 No. of Patients	No. of Deaths	LVED 13–19 No. of Patients	No. of Deaths	LVED ≥ 20 No. of Patients	No. of Deaths
One	43	0	17	1	5	1
Two	107	7	50	1	23	5
Three	86	1	56	1	21	5
Totals	236	8	123	3	49	11
		(3.4%)		(2.4%)		(22.4%)

TABLE 5. *Operative Deaths in 448 Patients**

Cause of Death	No. of Patients	Time of Death (days)
Myocardial Infarction	8	1-26
Low Output Syndrome	7	1-24
Arrhythmia	3	1-10
Miscellaneous†	10	1-38
Total	28	1-38

* Within 30 days or never left hospital (only one patient was > 30 days)

† Technical Factors: 5
Infection: 2
CVA: 1
Pulmonary Embolism: 1
Sup. Mesenteric Artery Thrombosis: 1

TABLE 6. *Status of Angina in 383 Patients Following Operation*

Status of Angina	Number of Patients	% of Total
Symptomatic Improvement No angina: 215 (57%) Less angina than preop: 114 (29%)	329	86%
Angina Equal to Preop	48	12%
Angina Worse than Preop	6	2%

gram or from serum enzyme concentrations following operation.

Late Evaluation

Relief of Angina. Information regarding status of angina was available on 383 of 420 patients surviving operation (Table 6). Angina was either completely relieved or significantly improved in 329 patients, 86% of the entire group. It was considered unimproved, equal to that before operation, in 12% and actually worse than before operation in 2%. Usually any type of chest pain was interpreted as possible angina, so the actual frequency of angina may be overestimated, being confused with complications of the sternotomy incision such as fracture of costal cartilages and similar musculoskeletal disorders.

Angiographic Studies of Graft Patency. As mentioned earlier, coronary angiography was strongly recommended on a routine basis 6–12 months following operation. However, asymptomatic patients were naturally reluctant to have angiography again; so this could not be done in many patients. Forty-eight per cent of the group of 420 patients surviving operation were restudied, a total of 201 patients. Frequently the angiograms were done because of reappearance of angina. When angina returned after being absent, it was almost always found that either a graft was occluded or severely narrowed. Very rarely was disease in another artery found as the explanation. Almost never were all of the grafts inserted found to be normal.

Seventy per cent of the angiograms were done within the first year after operation, usually 6–12 months afterward, 19% between one and two years, and the remaining 11% at a later time. Almost all of the significant angiographic data are with venous bypass grafts. Only limited data are available in this 1968–1972 group regarding patency of internal mammary artery grafts though results thus far indicate a patency rate well above 90%. The results are shown in Table 7. Thirty-six single bypass grafts were studied, finding a patency rate of 81%. With 86 double bypass grafts, 51% had both grafts patent, 41% only one patent, while 8% had both occluded. Overall patency in this group for all vein grafts inserted was 72%. Seventy-nine patients with a triple bypass were studied. Thirty-eight per cent of these had all three grafts patent, 34% had two patent, 24% had one patent, while only 4% had all three occluded. Hence, this group was similar to the double bypass group, with an overall patency of 69% for all vein grafts inserted.

These data probably represent some of the lowest patency rates that can be expected with vein grafts, for at operation an aggressive policy was pursued of attaching grafts to most arteries explored, even those diseased and as small as 1 mm internal diameter. It was realized that such grafts might well occlude but rather than simply ligate an artery or attempt to suture the arteriotomy, a graft was usually attached once an arteriotomy had been made. This policy, of course, resulted in a greater frequency of thrombosis and a lower patency. Data were not available to correlate patency rate with such significant factors as diameter of the coronary artery (1.0, 2.0 mm, or greater) or with the rate of flow through the graft afterward.[23]

In the 201 patients studied there were only 17 in whom no grafts were patent. Of these 17, only three had no

TABLE 7. *Patency of Venous Grafts Found on Angiography 6-24 Months After Operation*

No. of Grafts Inserted	Total No. of Patients	No. of Grafts Patent				Overall Patency Rate
		0	1	2	3	
One	36	7 (19%)	29 (81%)	—	—	81%
Two	86	7 (8%)	35 (41%)	44 (51%)	—	72%
Three	79	3 (4%)	19 (24%)	27 (34%)	30 (38%)	69%

Note: 92 and 96% of patients with two and three grafts inserted respectively, had at least one graft patent.

angina. Nine felt that their angina had improved somewhat but remained to a significant degree. In the others, angina was either equal in severity or worse than that before operation. Previous studies have found a high inverse correlation between patency of vein grafts following operation and the persistence or recurrence of angina.[8]

Cardiac Function. The influence of bypass grafting on impaired cardiac function is not the purpose of this report, but in general, little influence of bypass grafting on cardiac function could be discerned in the 201 patients studied.[21] Unfortunately, patients with impaired ventricular function showed little change after bypass grafting, neither improving nor deteriorating. The failure to improve was discouraging, probably due to irreversible injury, but the lack of further deterioration raised the question of whether the insertion of bypass grafts had prevented further injury.[16]

Late Myocardial Infarction. Myocardial infarction occurred in 32 of the 420 patients surviving operation during the period of observation, and was fatal in eight. The cumulative incidence of late myocardial infarction is shown in Fig. 2, increasing to about 17% five years after operation. Figure 3 shows the five-year probability of surviving without myocardial infarction to be 73%.

Late Mortality. There were a total of 23 deaths following discharge from the hospital (Table 8). By comparison, there were 28 operative deaths, most occurring in 1968–1970; so the largest mortality in the series was at the time of operation, giving an overall operative mortality of 6%. As mentioned earlier, since the end of 1971 the operative mortality has remained less than 3%. The causes of late deaths are shown in Table 8.

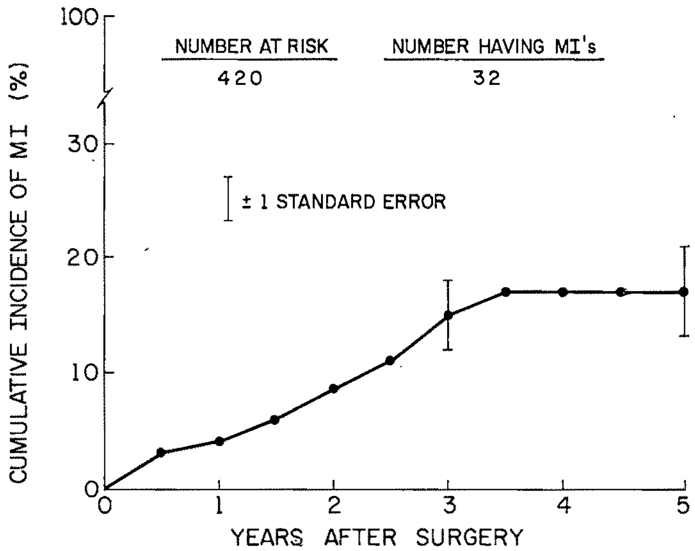

FIG. 2. The cumulative incidence of myocardial infarction in five years following surgery in patients surviving operation. Patients not experiencing myocardial infarction who died were withdrawn alive at the time of death.

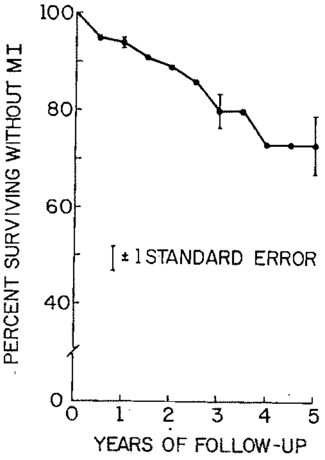

FIG. 3. Five-year survival without myocardial infarction. The curve shows that patients surviving operation had a 73% chance of living five years without myocardial infarction.

Figure 4 shows that when all deaths are included, including operative deaths and deaths from non-cardiac causes, the five-year survival is 77%. If 15 non-cardiac deaths are withdrawn alive at the time of death, the five-year survival is 81%. The expected five-year survival for this study group based on U.S. Population Life Tables (1965) is 92%. Also shown in Fig. 4 is the five-year survival of a group of patients reported by Sones who had coronary disease confirmed by angiography, either single, double, or triple disease, but were not operated upon. The five-year survival was 66%.[2]

The question of bypass grafting for single vessel disease has been particularly scrutinized because this group has the most favorable prognosis with conservative management. It is significant that in this series there were no operative deaths whatsoever following a single bypass graft in the last four years of the study. Four patients died at a later time. The cause of death in one was from non-cardiac causes, while in the other three it was due to disease in other vessels. In no instance was death due to failure of the single bypass graft. Hence, the operative hazard of a single bypass graft is extremely small and the likelihood of sustained benefit great.

TABLE 8. *Causes of Late Death in 420 Patients Surviving Operation*

Cause of Death	Number of Patients	Time of Death Postop (months)
Myocardial Infarction	8	1½ 37
CHF	2	12½ and 33
Arrhythmia	1	3
Death Related to Operation	4	3 46
Miscellaneous*	8	1 33
Total	23	1 46

* Miscellaneous: Infection: 3 CVA: 1 Suicide: 2 Cancer: 1 Pulmonary Insufficiency: 1

In Table 9 the 15 late cardiac deaths are analyzed in relation to two questions: whether all diseased arteries were bypassed at the original operation and the status of the grafts on late angiograms. Unfortunately the crucial data of graft patency at the time of death is unknown in seven of the 15. Hence, definite conclusions cannot be made. It may be significant however, that there are only two patients in the group of late deaths, in whom all three grafts inserted were found patent on subsequent angiography. One of these died 20 months after angiography; so the subsequent development of a graft complication could not be excluded.

Discussion

Operative Considerations

Operative Mortality. As shown in Table 1, operative mortality steadily decreased from an initial high level of 28% in 1968 to the low level of 2.2% in 1972. This decrease was primarily related to changes in operative technique, not to patient selection. The only patients excluded were those with chronic congestive failure after initial experiences had shown both a prohibitive mortality and failure of significant improvement in survivors. However, patients with substantial injury of the left ventricle from previous infarction were consistently operated upon. As shown in Table 2, approximately half of the patients had significant signs of cardiac injury beforehand, in many of whom the end-diastolic pressure was elevated (Table 4).

The principal factors improving operative mortality can only be estimated as these evolved gradually. These are probably the avoidance of long periods of cardiac ischemia, maintenance of a normal blood pressure during operation, decompression of the left ventricle with monitoring of the left atrial pressure during operation, and meticulous avoiding of air embolism. The low mortality has not been related to a short perfusion time, for periods of perfusion of two to three hours have been common with a triple bypass, and a perfusion even for four hours has had little morbidity.

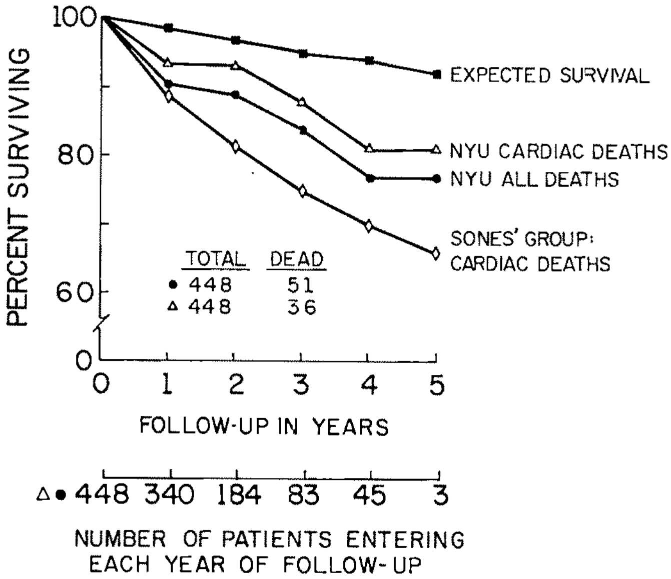

FIG. 4. Life-table survival curves. Expected survival is determined for the same age-sex-race composition as the group under study using U.S. Life Tables for 1965. Survival curves for cardiac deaths (NYU and Sones' group) considered non-cardiac deaths as withdrawn alive at the time of death. Cardiac deaths included deaths due to myocardial infarction, congestive heart failure, arrhythmia, low output syndrome and reoperation for coronary bypass.

TABLE 9. *Relation of Late Cardiac Deaths to Adequacy of Operation and Graft Patency*

Cause of Death	Adequacy of Operation	Graft Patency
1. Arrhythmia	Yes	unknown
2. CHF*	No	unknown
3. CHF	Yes	3/3
4. MI†	Yes	1/3
5. MI	Yes	unknown
6. MI	Yes	unknown
7. MI	Yes	unknown
8. MI	Yes	unknown
9. MI	No	unknown
10. MI	No	1/2
11. MI	Yes	3/3
12. Death related to reop	Yes	1/3
13. Death related to reop	Yes	occluded
14. Death related to reop	No	occluded
15. Death related to reop	Yes	occluded

* CHF: congestive heart failure
† MI: myocardial infarction

The frequency of operative infarction was measured only in selected samples, but was well under 10%. The absence of a high operative risk in patients with serious impairment of ventricular function may be partly due to the low frequency of operative infarction. Patients with extensive injury of the left ventricle are probably much more vulnerable to operative infarction than those with a normal ventricle beforehand.

As mentioned earlier, impaired ventricular function and an elevated end-diastolic pressure was not associated with a high late mortality (Table 3). This supports the policy of operation upon such patients, realizing that ventricular function will probably not improve but further injury may be prevented. Similar data have been reported by others.[13,16] Actually, a strong thesis can be made for operation upon such patients, for the reserve of functioning left ventricular muscle has already been seriously compromised. Such patients are much less able to withstand loss of additional muscle from a future infarction than those with a normal ventricle.

As shown in Table 1, a double or a triple bypass was performed on most patients. However, as mentioned earlier, experiences with a single bypass graft were particularly favorable. There was no mortality in the last four years, and no late deaths resulted from failure of the single grafts. Hence, although the five-year mortality for non-surgical patients with single vessel disease reported by Sones is only 14.6%,[2] the outlook following a single bypass graft may be even more favorable.

Improvement in Angina. As noted in many reports, the immediate response after operation in the majority of patients is either elimination or striking improvement in angina. This was true in 86% of this group (Table 6). Angina of course is a subjective sensation, difficult to evaluate with precision, but is the principal symptom of myocardial ischemia. As mentioned earlier, once angina disappeared after operation, its reappearance at a later time almost always indicated stenosis or occlusion of a previously functioning graft. Progression of atherosclerosis in arteries without significant disease at the original operation was an uncommon cause.

Patency of Vein Grafts. The overall patency of vein grafts was 71%, 315 out of 445 grafts studied (Table 7). It was striking, however, that the occlusion of vein grafts was sporadic, and few patients, only 4–8% of those undergoing double or triple bypass grafting, were unfortunate enough to occlude all grafts inserted. Hence, the likelihood of a patient remaining with at least one functioning graft for two years after operation was well over 90%. The recent report by Grondin and associates[10] of serial angiographic studies one to three years after operation showed that most occlusive changes developed in the first year after operation, with patency rates three years following grafting being similar to those one year after operation.

A detailed analysis of the cause of vein graft closure is beyond the scope of this report, but certain observations seem pertinent. The occurrence of segmental occlusion, with comparatively normal segments proximally and distally, is suggestive of a local injury from either trauma at the time of procurement of ischemia during preservation. Szilagyi[22] has emphasized that warm ischemia time for vein grafts may be important because of the smooth muscle in the wall of the vein. This forms the basis of our current practice of keeping vein grafts in a 4 C balanced electrolyte solution until used. The role of adhesions in obstructing grafts was impressive in some patients with a chronic pericarditis which obliterated all grafts within a few months. Reoperation upon several such patients found two distinct findings. First, adhesions were often severe where the grafts were not covered by pericardium but left free in the pericardial cavity, while segments of the graft covered by pericardium were unusually free of adhesions. Following this observation, grafts have been covered with pericardium in almost all patients. The second observation was that straight grafts were peculiarly vulnerable to intermittent tension from the cyclic contraction and relaxation of the heart, with the grafts stretching in diastole and relaxing in systole. A few patients showed a striking proliferation of collagen when adhesions permitted intermittent tugging on the graft, similar to formation of a keloid in a surgical incision crossing a joint. Subsequent to this observation, grafts have been placed in a curved, sinusoidal fashion over the epicardial surface, carefully attaching them with sutures five cm apart. The apposition of lymphatics in the adventitia of the vein graft to those in the epicardium is an additional theoretical advantage.

Grafting combined with endarterectomy was disappointing in a few patients, and subsequently has been almost abandoned. Grafting a vessel as small as 1 mm, with a flow rate of 20 ml or less, was also disappointing and is probably of limited value. A side-to-side anastomosis to these small arteries is now being explored.

Though not the purpose of this report, results with anastomosis with the internal mammary artery to the anterior descending were quite encouraging. This operation was originally developed at New York University by Green and Tice in 1968.[20] During the past two to three years, this artery has been used in over 80% of patients operated upon.[11] Double internal mammary grafts however have not been widely used.

Late Myocardial Infarction and Death. As mentioned earlier, only 32 out of 420 patients surviving operation subsequently developed a myocardial infarction during the period of observation (Fig. 2). A life-table analysis of these data found the probability of surviving five years without an infarction to be 73% (Fig. 3). The overall five-year survival of 77%, including both operative deaths and deaths from non-cardiac causes, (Fig. 4), is most encouraging as it compares to an expected 92% for a similar U.S. population group. If deaths from non-cardiac causes are excluded, the five-year survival is 81%. The best available data for comparison of our results with non-surgical therapy are those of Bruschke and Sones at the Cleveland Clinic, who found, in a consecutive group of 590 cases of coronary disease not operated upon, that the five-year cardiac mortality was 34%, or a survival of 66% (Fig. 4).[2] They reported a five-year cardiac mortality of 15% for single vessel disease, 38% for double vessel disease, and 54% for triple vessel disease. Comparison of the overall five-year cardiac survival of 81%, in our series, with that of Sones' overall five-year cardiac survival of 66%, although favorable, is nevertheless probably adversely influenced by the fact that most patients in our series had double or triple coronary disease. A more precise statistical comparison would be to compare single, double and triple coronary disease treated by surgical or nonsurgical methods. Furthermore, the surgical results now being obtained will probably show much better long-term results because of improvements in operative technique. A more complete bypass operation is being performed, grafting nearly 85% of all diseased vessels, and the operative mortality is much less, under 3%. Probably the frequency of subclinical infarction is similarly decreased.

In patients developing either a late myocardial infarction or dying from cardiac causes several possibilities can be considered. If all diseased major coronary arteries were effectively grafted, death would represent a failure of bypass grafts. It seems significant that this apparently occurred in only *two* patients in the entire group of 448, both of whom had triple bypass grafts which were subsequently found patent on late angiography. The other general possibility to consider is whether the diseased coronary arteries had effective bypass grafts at the time of deaths. An ineffective bypass could result from either an incomplete operation initially or from late failure of a previously functioning graft. A third possibility is the development of additional occlusive disease in arteries with physiologically insignificant disease at the time of operation. As mentioned earlier, these possibilities are briefly considered in tabular form in Table 9, but few conclusions can be reached as the status of the grafts was unknown at the time of death in seven patients.

Long-term Considerations

1. *Indications for Operation.* At present there are widely varying approaches to the use of bypass grafting for coronary disease, ranging from bypass grafting for asymptomatic patients following angiographic demonstration of severe stenosis to those who employ grafting only as a last resort or virtually not at all. This series includes predominantly those with severe angina not responding to medical therapy. It seems unlikely that everyone with occlusive coronary disease should require a bypass graft because of the great capacity of many individuals to develop collateral circulation. The crucial question of course is whether or not a patient can develop adequate collateral circulation around an area of occlusion. Clearly many cannot, or otherwise there would not be such a high fatality rate from coronary artery disease. This widely varying capacity of patients to develop collateral circulation is partly responsible for the broad range of clinical syndromes in coronary disease.

2. *Harm from Bypass Grafting.* The operative risk of bypass grafting has decreased to a surprisingly low level, less than 3% in many centers, indicating its great safety. The occurrence of operative infarction in some series as high as 20%, is distressing and surely can be eliminated with a better understanding of cardiac physiology during bypass. The frequency of infarction has been small in specific groups in this series, but the future goal should be a frequency well under 5%. Apart from operative injury, the theoretical hazard with a bypass graft is inhibition of the development of collateral circulation. In addition, several studies have found that closure of a proximal area of stenosis is accelerated because of change in flow rate. Hence, a graft may not only accelerate the progression of a proximal stenotic lesion but at the same time inhibit the development of collateral circulation. Theoretically, then, if a graft becomes occluded, a patient might be even worse than without operation, having occluded his stenotic artery without developing collateral circulation. Clinically, this has been quite unusual. Apparently graft closure, when it does occur, is at a slow enough rate to permit development of a collateral circulation. Relatively few patients who have occluded previously inserted grafts have required reoperation.

3. *Prevention of Myocardial Infarction with Bypass Grafting.* The frequent occurrence of a fatal myocardial infarction either during sleep, rest, or mild physical activity, rather than during intense physical activity, suggests that relatively small changes in blood flow may precipitate infarction in an area of severely ischemic myocardium. A common finding at autopsy following a fatal "heart attack" is extensive occlusive disease but no acute change, such as hemorrhage into an atherosclerotic plaque, which might explain the sudden death. Thrombosis in an area of stenosis may be found in some patients, but Roberts has recently published an intriguing hypothesis that the thrombus may develop as a *consequence* of infarction rather than causing it.[17]

The probability that a small decrease in coronary blood flow, in the range of 50–100 ml/min, may precipitate myocardial infarction indicates that a bypass graft to a critical ischemia area could have a profound influence on preventing infarction and prolonging life.

4. *Future Goals.* At present two major goals for future studies seem clear. First, the objective should be to develop a method of coronary bypass grafting that will produce a consistent patency rate of at least 80% five years after operation. This has been achieved by several investigators with venous bypass grafts for femoral-popliteal disease over the past 15 years; so this goal is theoretically attainable.[5,6] It appears that an arterial graft has a much better probability of remaining patent, but a comparison of long-term results between arterial and venous grafts is not yet available. Possibilities such as the use of a radial artery or the splenic artery have been explored by some investigators.[3,7] If a patency rate of 80% for five years can be achieved, it seems highly probable from the data presented in this report that

significant prolongation of life and protection from myocardial infarction can be achieved. Answers will come primarily from comparative prospective studies of medical and surgical therapy, preferably randomized. A nonrandomized comparative study has recently been published by McNeer and Rosati, analyzing nearly 90 variables in 402 patients treated medically and 379 patients treated surgically. A particularly ominous prognosis was found in patients with triple disease and an abnormal ventriculogram, with a two-year mortality between 61% and 76% with medical therapy.[15] For disease groups to be comparable, certain specifications seem crucial. An angiogram must obviously be obtained. Otherwise the great overlap in clinical syndromes between single, double and triple coronary disease makes comparative data almost impossible. A second consideration is the presence of symptoms, for there is widespread individual variation in the ability to develop collateral circulation. A patient who becomes asymptomatic after occlusion of a major artery by development of adequate collateral circulation is surely not comparable to one who remains symptomatic from occlusion of a similar artery because collateral circulation is inadequate. Hence, the need exists for randomized studies of comparable patients. Such studies are currently being developed by the National Institutes of Health. Only by objective comparison of such data over a period of years can decisions be made regarding the immense logistical question of widespread use of bypass grafts for coronary disease in the mildly symptomatic or asymptomatic patient.

Acknowledgments

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DISCUSSION

DR. DONALD BRIAN EFFLER (Cleveland): We have taken a little different philosophy and attitude about the need for revascularization surgery than the one expressed by Dr. Spencer and his colleagues. We believe that the man with the normal ventricle and with severe angina and threatening disease is probably more deserving of surgery than the man who has already had multiple insults to his ventricle. In other words, the normal ventricle that is now threatened has more at stake than does the one that has already had multiple infarcts with attendant impairment of function.

Since 1967, Dr. Sones and his colleagues have made a retrospective study of people who were considered ideal candidates for revascularization surgery; these patients had good ventricles, but had coronary disease described as single, double, and triple vessel in type. Their retrospective analysis of life expectancy follows this pattern: if they had single vessel disease, within five years 20% of them had died, within the same period of time those with double vessel disease suffered a 40–45% expected mortality, and the triple vessel disease patients faced a dismal 70% death expectancy within five years. All as a result of their coronary artery disease. This is certainly an unimpressive testimony for medical therapy because all of these patients were private patients and all were given the benefit of the best we had to offer from the standpoint of modern medical treatment.

Beginning in 1967, when René Favaloro did our first interposed saphenous vein graft, 4600 patients were operated upon with bypass graft techniques by the end of 1972. In the past year, there has been an additional group of 1573 patients—this is the 1973 record—and as mentioned by Dr. Spencer, the mortality rate with experience gets lower and lower. There were exactly 15 deaths in this 1973 group, giving us a mortality rate of slightly less than 1% overall. We believe this is important and necessary. In other words, the surgical treatment of coronary artery disease requires a "cheap operation," cheap from the standpoint of risk to the patient.

It was already mentioned that the mammary-coronary anastomoses seemed to have tremendous promise, perhaps more than the saphenous vein grafts; and this appears to be correct. During 1973 there were 464 patients in the Cleveland Clinic series who were operated upon with mammary-coronary techniques; either mammary-to-coronary anastamosis alone or mammary-coronary anastamosis combined with a single vein graft. By good fortune, no patient died during this particular period, giving us a zero mortality rate. Another factor of importance is the low postoperative myocardial infarction rate which runs less than 4%.

Postoperative angiographic studies, as Frank Spencer has already pointed out, suggest a graft patency rate in the neighborhood of 80%. If you will look at our experience between 1967 and 1972, there were 1152 grafts restudied. In the year 1972, 1100 grafts were assessed by postoperative angiography. The overall patency rate is approximately 80% throughout both series. Actually, this is not a precisely correct figure, and it is probably conservative for two reasons. First of all, the patient most likely to be studied after surgery is the one who is not doing well; this will be the man who has had abrupt recurrence of his angina caused by primary-graft thrombosis. Secondly, many patients receive more grafts than they actually need for relief of symptoms; when a patient with triple vessel disease receives three grafts and obtains the desired result, even though one graft may have closed, it seems a bit silly to classify him as an "incomplete result" because of his postoperative arteriography. Arithmetically this individual has a 66.6% angiographic result even though he enjoys 100% clinical rehabilitation. If we look at the results in patients who undergo single vein graft surgery, the patency rate here is between 92–94%. Therefore, it will be statistically more significant to classify grafts as "primary" or "supporting" since the individual patency will have considerable variation in significance.

From the standpoint of relief of symptoms, as has already been alluded to, there is no question that revascularization surgery by the bypass techniques is extremely successful. The retrospective study done by Shirey shows that the preoperative patients, the great majority of them, were Class II, III and IV. After surgery these patients were predominantly angina-free (Class I). The majority of them had no angina of any kind, nor could angina be induced on stress test; we think this is very significant.

After our initial experience, as results improved and enthusiasm escalated, there was a natural tendency to put in more grafts with individual operations; nevertheless, it would appear that we have tended to level off since 1970, and the graph shows 65% of patients receive double or triple grafts. It was suggested by Dr. Spencer that more people probably need more grafts; triple, quadruple, and so forth. We're not entirely sure that this is correct. Whereas the majority of patients operated upon by the Cleveland Clinic team have multiple grafts, the larger segment will have two; quadruple grafts, quintuple, and the like, seem to be less and less frequent.

Perhaps the most important factor relative to revascularization surgery is longevity. If we compare the Webster-Moberg series that describes the fate of patients with single, double, and triple vessel disease treated medically, it would appear that the patients who undergo revascularization surgery do appreciably better. Sheldon's analysis of postoperative survival rate in over one thousand patients in the Cleveland Clinic series suggests that the life expectancy curve parallels that of patients who suffer from single vessel disease. This has been interpreted by some cardiologists as an indication that there is no need for surgery in single vessel disease, but I do not think this is correct conclusion. In Sheldon's series of postoperative patients there was no correlation between success and failure of the operative result—only survival. It is reasonable to assume that somewhere in the neighborhood of 15% of these postoperative patients have primary graft occlusions. Therefore, it would be far more significant to contrast *successful* postoperative cases with the Webster-Moberg curves.

When the surgical team has been established and the operative procedure has been standardized and when all concerned arrive at a sensible system for selection and rejection of the candidate for revascularization surgery, then revascularization surgery will be performed with a hospital mortality rate of in the neighborhood of 1–2%. This standard of surgical performance has been achieved already in many community hospitals throughout the United States as well as major surgical centers. Dr. Spencer and his colleagues deserve commendation for this excellent report; as various teams gain experience, there seems to be less and less major differences of opinion. There seems little doubt today that the surgeon will continue to play a dominant role in the treatment of the patient who suffers from ischemic heart disease.

DR. DAVID C. SABISTON, JR. (Durham): It is remarkable to observe the consistency with which Dr. Spencer makes presentations of excellence, and I would like to commend him and his associates for this fine study. Moreover, when one reads the complete manuscript, it is impressive to note the additional data which further support the points which he has just made.

Most of those interested in myocardial revascularization agree that there are numerous problems which remain, and I should like to comment briefly about computer analysis and interpretation of some of the major points which Dr. Spencer raised this evening.

Recently, Dr. McNeer, working with the computer group, has completed a study of 781 consecutive patients seen at Duke with angina pectoris. In each instance, the diagnosis was confirmed by coronary arteriography and an obstructing lesion of 70% or more of one of the major coronary arteries was demonstrated. All patients were classified with the entry of some 89 different parameters into the computer. These entries varied from clinical manifestations at one end of the spectrum to specific figures of cardiac performance at the other.

Of the 781 patients studied, 402 were treated medically and 379 by surgery. At the end of the second year, the survival rate for all patients in the study was slightly higher in the surgically treated group, but it is impressive that twice as many of the survivors in the surgical group are now completely free of pain.

Moreover, in a group of 169 equally matched patients with three vessel disease and evidence of angiocardiographic abnormality of left ventricular contraction, approximately half of these patients were managed medically and half surgically. At the end of the first two years, 76% of the medically treated group had survived, whereas in the surgically managed group the survival was 90%.

With the passage of more time, it is likely that the surgical group will show an increasingly favorable survival, although this yet remains to be seen. However, it is already apparent that in certain groups these computerized data can be identified preoperatively and aid in the selection of patients in whom surgery is apt to be the most beneficial. In addition, this approach will identify those in whom it can be statistically predicted that life expectancy will be increased.

DR. JOHN L. OCHSNER (New Orleans): I rise to give some support to the internal mammary as the principal conduit today.

(Slide) With proper preparation of the internal mammary, one can achieve as much as 300 cc of free flow per minute. These are our postoperative angiograms, all of these over a year. As you can see, in the vein bypass 29% either occluded or narrowed postoperatively.

By contrast, of the 88 patients who had an internal mammary and have been followed and studied, only one is occluded and it was occluded during the study by a catheter that dissected the internal mammary, and two are narrowed; both technical errors.

The internal mammary can be used, as Dr. Spencer showed, not only to the anterior descending (slide), but it can be used to the right; (slide) it can be used to the circumflex; (slide) and it can be used as a free graft to any vessel on the myocardial surface.

I think in this day and time, with our present-day knowledge, the principal graft should be the internal mammary.

DR. GEORGE COOPER MORRIS, JR. (Houston): Our experience has been essentially similar in most respects (slide) to Dr. Spencer's. These particular statistics are my own, and you will see that some 94% of patients have at least one open graft and graft occlusion rate was 12%. However, I think the overall patency rate is probably better than these statistics would reveal. In the last three years only those patients who are essentially squeaky wheels, as it were, were studied, together with some of the patients who fall into interesting groups such as congestive heart failure.

(Slide) Frank Spencer has been interested in the bad ventricle, and has talked about this problem for several years. Our experience has been somewhat different in terms of the operability and the long-term results. The reduction in end diastolic pressure has not been remarkable. In some it has been good; in others it has been minimal. But clinical results have been outstanding.

Here you see some improvement in the ventriculogram postoperatively, but the fall in diastolic pressure has been modest.

(Slide) Here is a patient who was essentially bedfast before operation, and his end diastolic pressure has not fallen after operation; and yet for three years he has never missed a day's work. This man's congestive heart failure was documented at Dr. Effler's clinic.

(Slide) Here is another example of single vessel disease with what appears to be an aneurysm, but was simply a poor apex. Even without resection of any myocardium, you can see the improvement with a single bypass.

Formulas and computers have been of little help to me in trying to ascertain which patients with very bad ventricles will come off pump. The best guideline to me has been somewhat simplistic, but has worked very well. That is visualization of total occlusions, particularly of a major left coronary artery, which will accept a distal bypass. Patients with diffuse disease, with a bad ventricle, without total occlusion of main coronary arteries, will very likely do poorly.

(Slide) One of the most striking findings has been work status in patients with bad ventricles and preoperative congestive failure compared to the overall group of bypass patients. It is difficult to argue with return to work status, and you can see that there is not a great deal of difference between the two groups.

Similar to Frank Spencer's experience, the attrition rate yearly in terms of death has been essentially the same in these patients with the bad ventricles and patients with angina alone; and that has been 2½% per year, exactly the same.

The hospital mortality in those with congestive failure preoperatively has been 8½%, compared to 3½% for the usual group, and 0.7% for those with single vessel disease and good ventricles.

DR. JACK A. CANNON (Phoenix): In the last few years, the surgical potential in the direct arterial surgical attack on obliterative atherosclerosis of the coronary arteries has been "suddenly" discovered. Dr. Spencer has mentioned in his paper that he envisions the "curative" surgical correction of these atherosclerotic lesions of the coronary arteries may be attainable. I note that after *palliative* surgery to the arterial tree at *any* level, subsequent atherosclerotic involvement has been recorded in *any* type of reconstructive endeavor. This involvement includes endarterectomy, homologous arterial bypass, Dacron bypass, and autologous vein bypass. I ask Dr. Spencer, how does he envision the possibility of a curative result from a palliative surgical endeavor?

It has been my experience in the attempted palliation of coronary obliterative atherosclerosis that lesions of the left coronary tree are likely to be diffuse and to involve vessels of smaller caliber than when the right main coronary is involved. I note also that reconstructive direct surgical endeavor directed to the left anterior descending coronary and branches of the left circumflexcoronaries involve vessels which are smaller in diameter and more diffusely involved. I note that the re-occlusion rate of reconstructions of the left anterior descending coronary and the left circumflex artery seem to be higher than such reconstructions to the right main coronary. I note also that long-term results seem to be more affected by the excellence of intercoronary collateral in the individual case than by the nature of the technical intervention. I am unable, in evaluating any data so far—especially that presented by Dr. Spencer—to recognize *any* advantage of the use of internal mammary artery versus the autologous saphenous vein as implied by Dr. Spencer in his analysis of his series.

I suggest that his improved results may be more related to the improved technique afforded by the use of the operating microscope and even the steady-handed, near-sighted young surgeon in performing these meticulous anastomoses, rather than some mysterious quality of the difficulty harvested, tenuously and uncertainly prepared, frequently damaged internal mammary artery. I ask Professor Spencer to speak of these considerations.

I note that in this excellent paper, Dr. Spencer makes no mention of electromagnetic flow meter measurements of the results of reconstructive coronary arterial surgery. It is true that measurements of flow through the internal mammary artery are difficult since the diameter of the vessel to be measured is usually less than the 2–3 mm minimal diameter of the smallest flow probe accurately available. I note that I am extremely unhappy with a post-reconstruction flow rate of less than 50 cc/min. This rate is rarely obtained, even when measurable, with internal mammary artery reconstruction. Left-sided autologous vein reconstructions are not surviving the test of time. Time has not yet proven the superiority of internal mammary artery reconstructions. Would Dr. Spencer please speak of these considerations?

Finally, since there can really be no question that coronary reconstruction for atherosclerosis is palliative in nature, I ask: Should we seriously be considering surgical attack against the cause of the disease. Earlier in this program, Dr. Varco and his group reported on the effective, obligatory, non-escape lowering of serum cholesterol and serum triglycerides in patients with symptomatic atherosclerotic lesions. His series involved patients with abnormally elevated serum cholesterol and triglycerides. Human races with no incidence of atherosclerotic disease show serum cholesterol levels in the 100–150 range with serum triglycerides of a correspondingly reduced level. Lethal atherosclerosis is epidemic in western "civilized" man whose "normal" serum cholesterol is considered to be 180–300 mgm%. I ask Dr. Spencer:

Should ileal shunt for the prevention of this disease in patients with potentially lethal coronary atherosclerosis be considered as implied by the results of Dr. Varco and his group?

Dr. Frank C. Spencer (Closing discussion): I think the many contributions by Dr. Effler and his group at the Cleveland Clinic should be emphasized. They have clearly demonstrated the wide applicability of the operation and the very low mortality. Before 1966 any operation on the left coronary artery had a mortality exceeding 50%. That was only eight years ago; so the progress in achieving the present low mortality is great.

Dr. Effler's concept of a double bypass for triple vessel disease is certainly plausible. Theoretically, after two grafts have been inserted for triple vessel disease, the patient may have the subsequent prognosis of someone with single vessel disease, provided both grafts remain patent. It seems reasonable that it would be unwise to prolong an operation unduly to insert an additional graft, though in the majority of our patients all diseased arteries have been bypassed.

I feel certain that much is yet to be learned about the cardiac physiology and intercoronary blood flow during bypass, while the heart is decompressed, the ventricle fibrillating, and intramural tension considerably altered. All of these factors may influence collateral blood flow. One reason for the very low mortality reported by Dr. Effler's group may be the relatively short bypass time with most patients.

Regarding Dr. Sabiston's comments, I would like to emphasize the great value of computer analysis for this disease with so many variables. In their recent publications, a computer analysis of over 80 variables clearly defined a sub-group of patients with vessel disease and an abnormal ventricle, with a two-year mortality near 25–30% with nonoperative treatment. The analysis clearly demonstrated that unless sub-groups were separated, the overall influence of a method of therapy was difficult to determine.

I agree completely with Dr. Ochsner's enthusiasm and emphasis on the use of arterial grafts, especially the internal mammary artery. I consider the mammary probably an ideal graft, except it is difficult and tedious to mobilize in some patients because of its size and friability. However, all considerations about the ideal graft remain hypothetical until data demonstrate at least 80% patency after five years, comparable to data obtained with bypass grafts for femoral-popliteal disease.

The internal mammary artery is of particular interest for the question of bypass grafting for isolated occlusion of the anterior descending coronary artery, a group often not operated upon because of the favorable prognosis. From the surgical standpoint, however, the operative risk approaches zero, the relief of symptoms is dramatic, and the patency shown by several groups ove a year after operation with the internal mammary artery is ove 95%. Hence, the operation very closely approaches "a cure." W have had no failures with single bypass grafts in our patient with disease limited to the anterior descending coronary in th past four years.

Dr. Morris emphasizes the difficult problem of the patient wit substantial injury of the left ventricle before operation. It seem that the normal human heart has a reserve of about 30% of th left ventricular muscle mass. Cardiac function remains fairl good until this limit is exceeded, but when loss of muscle mas approaches 30–40%, congestive failure appears, becoming intractable with more extensive injury. Hence, both the hazard of operation and the likelihood of benefit in patients with extensive injur of the left ventricle is increased. On the other hand, the patien has a very small safety margin; even one additional small infarc may precipitate chronic congestive failure. Bypass grafting i such instances, if successful, may possibly avoid further injury an protect from the end-stage disease of intractable failure, currentl treatable only by cardiac transplantation.

I cannot answer most of Dr. Cannon's question. We always us a flow meter at operation, though there is considerable uncertaint about its reliability. Flow varies, of course, with blood pressure vasomotor tone, and other factors. It is a valuable guide, howeve in demonstrating the capacity of the vascular bed beyond th graft, and is especially useful if re-operation is considered for a occluded graft months later. He correctly emphasized the important basic problem of the underlying atherosclerosis. One o the dividends of the bypass operation is that a base line i clearly defined, from which future efforts to control the atherosclerotic process can be measured. The grim fact at present i that nothing in medical therapy has yet strongly influenced th course of atherosclerosis when evaluated in randomized studie over a period of five years.

In conclusion, I want to emphasize again that answers wil come not from debate, but from careful accumulation of significant data over a long period of time. This is a major and awesome responsibility of all investigators in this area. The presen frequency of disease indicates that there are probably at least fiv million American males with significant occlusive disease of th coronary arteries, who would be theoretical candidates for a prophylactic bypass graft. This five million far exceeds the frequency of any other major disease in the American population The logistics, the expense, the training, the facilities all inheren in a decision of this magnitude are enormous. Hence, the grea responsibility for careful accumulation of data in reaching a clea decision is evident.

Cardiac Trauma:

Clinical and Experimental Correlations of Myocardial Contusion

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Clinical and experimental observations in myocardial contusion have been correlated. Cardiac arrhythmia is always an important consequence and may be fatal. Reduction in cardiac output often accompanies significant cardiac injury. The coronary arterial circulation is not interrupted and is generally enhanced to the area of injury. Healing of the injury under these circulatory conditions may result in patchy scarring and peculiar adynamic areas of myocardium. Early diagnosis of myocardial contusion may be aided using radionuclide imaging with ^{99m}Tc-Sn-polyphosphate.

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IN THIS AGE of automobile travel and mechanization of industry and agriculture, injury of the heart due to closed chest trauma has become an important clinical entity. Myocardial contusion is much more frequent than clinically recognized or current medical statistics indicate[9,14] because of low index of suspicion, physiologic importance of easily recognizable associated injuries, and nonspecific diagnostic techniques. Burchell's couplet typifies the problem of myocardial contusion:

> . . . and always with a heart contusion
> arise both doubt and much confusion.

Parmley[21] stated that it is a misconception to consider nonpenetrating trauma of the heart to be rare because myocardial contusion is usually well tolerated, and the clinical signs transient and difficult to recognize. The incidence of cardiac injury associated with closed chest trauma varies from 16% in an autopsy series reported by Leinoff[15] to 76% in a clinical series reported by Sigler.[26] Taking lower percentage figures, the national incidence of 150,000 cases per year would be a conservative estimate.[21]

The early studies of Kahn and Kahn,[12] and Bright and Beck[5] stressed the vulnerability of the heart to closed chest injury. The superficial position of the heart directly behind the sternum allows serious damage to be transmitted to the heart from an external blow even without obvious external injury. Yet, in a study of 90 patients with major blunt chest trauma,[2] the diagnosis of myocardial contusion was never established at the time of admission even though 20 had subsequent abnormal electrocardiograms and eight were shown to have cardiac injury at autopsy.

Cardiac injury due to nonpenetrating chest trauma is therefore quite common, but often the lesion is minimal and the morbidity may be slight.[21] Bright and Beck[5] stated: "It was surprising to us to see the amount of trauma that the myocardium could tolerate." The purpose of this study is to examine the physiologic and morphologic changes of myocardial contusion due to closed chest trauma. Correlations of clinical and experimental experience will be shown with emphasis upon the electrocardiographic, hemodynamic, and coronary vascular response to cardiac injury. An improved diagnostic technique using radionuclide imaging will be shown.

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Materials and Methods

Patient Group

Eight patients age 6–47 years were studied two weeks to five years following nonpenetrating injury to the myocardium. The mode of injury was closed chest trauma in five and missile wounds which did not penetrate the myocardium in three. The latter patients had injury of the heart by transfer of kinetic injury to the myocardium as the missile passed nearby, but not into the heart. In addition to the usual clinical evaluation, 12 lead electrocardiography and standard cardiac catheterization were performed in all patients. Cardiac output determination was established by the Fick principle. Selective coronary arteriography was performed in six patients and aortic root angiograms in two patients. Left ventricular angiography was performed in all patients and the outline of the left ventricle superimposed in systole and diastole for analysis of ventricular wall motion. Surgery was required in four of the patients. A ventricular aneurysm was resected in three patients (A.W., C.B., J.H.) 34–68 months after injury, and a ventricular septal defect with detachment of the papillary muscle of the tricuspid valve was repaired 21 days after injury (J.B.). Injured myocardium was excised and examined histologically in two patients. All of the patients survived injury and are presently alive with followup period two months to six years.

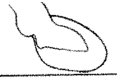
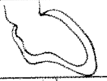
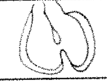
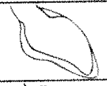
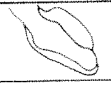
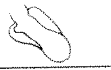
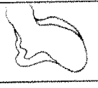
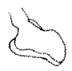
Experimental Group

Isolated myocardial injury was produced using the impact of a captive bolt hand gun to the intact chest wall of anesthetized dogs; 27 dogs weighing 16.5–21 kg were used in the study. Principles of humane care of animals were followed. A Super-Cash pistol (Accles and Shelvoke, Ltd., Birmingham, England), originally designed for the abattoir industry, was modified by attaching a 2-inch semi-elliptical steel disc to the end of the force transmitting piston. This device was held firmly against the chest wall at the point of maximum cardiac impulse. The lung was collapsed by temporary pneumothorax to protect it from injury as the weapon was discharged and kinetic injury transferred to the underlying myocardium. In 14 dogs, graded injury was produced by varying the powder load of the .22 calibre blank cartridge used in the weapon. These loads produced nominal velocity of 390–570 ± 45 feet/second of a 3/8-inch diameter 350 grain ballistic slug fired in a test device. Electrocardiogram lead II was monitored. Animals which died were immediately autopsied while others were sacrificed and examined at 24, 48, and 72 hours and at 14 and 21 days after injury.

Six dogs had hemodynamic studies prior to injury and at 15–30 minutes and 14–21 days after injury. Cardiac output was determined by injection of 2.5 mg indocyanine green into the right ventricle while blood was continuously sampled from the aorta through a Gilford Densitometer. Dye curves were analyzed by the Hamilton technique.

Seven dogs were sacrificed following myocardial contusion to examine the coronary circulation; these were examined immediately, 24 hours, 72 hours, and 7 days post injury. Heparin (1000 U/kg) was administered

TABLE 1. Patient data following myocardial contusion. Ventriculograms are superimposed in systole and diastole.

PATIENT	AGE	MODE OF INJURY	MONTHS AFTER INJURY	SYMPTOMS	CARDIAC INDEX L/min/M^2	ANGIOGRAPHY LEFT VENTRICLE	ANGIOGRAPHY CORONARY ARTERY
M.W.	46	Auto Accident	‹ 1	Respiratory Insufficiency	4.1		Normal (Increased to Apex)
J.S.	37	Auto Accident	‹ 1	Dyspnea Diaphoresis	3.1		Normal
J.B.	6	Kicked by Horse	‹ 1	Dyspnea Pulmonary Edema	1.7		Normal
L.T.	20	Gun Shot Wound	7	Asymptomatic Abnormal E. K. G.	4.0		Stenosis Diagonal LAD
A.W.	22	Gun Shot Wound	34	Pulsatile Chest Mass	3.4		Normal
C.B.	43	Auto Accident	36	Ventricular Arrhythmia	5.3		Normal
D.B.	47	Kicked by Cow	60	Fatigue Palpitations	1.8		Normal
J.H.	33	Mortar Wound	68	Embolus Femoral Artery	2.8		Normal

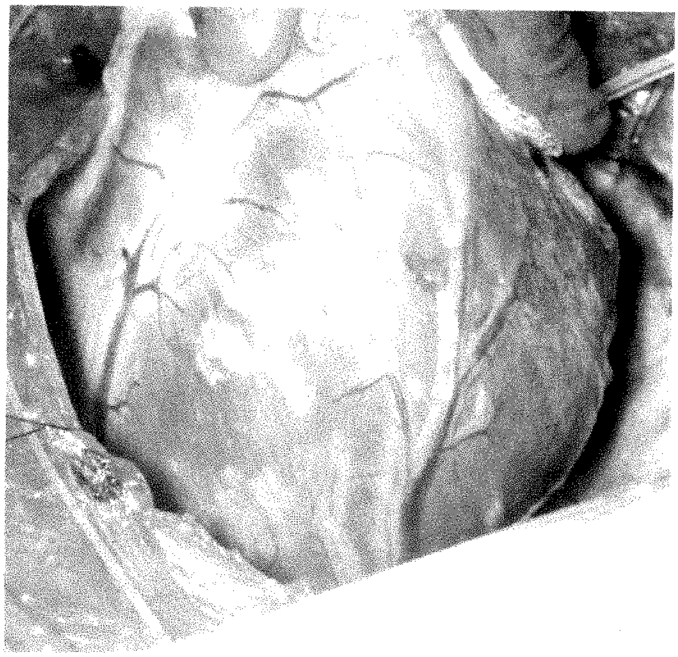


FIG. 1. Appearance of the heart after myocardial contusion. Patchy scarring of the myocardium is demonstrated in patient J.H. 68 months after injury. The apex is upturned to expose the posterolateral wall of left ventricle.

prior to sacrificing the animal with pentobarbital sodium. The heart and lungs were immediately removed *en bloc*. The ascending aorta was opened, and the coronary artery ostia directly cannulated and perfused with temperature reversible gelatin containing barium. The pressure of injection varied because the material was hand injected through a syringe, but as shown by Mautz,[17] would not be expected to fill blood vessels less than 70 microns in diameter. Temperature of the gelatin was above 90 C to maintain fluidity and after injection the hearts were immediately submerged in water at 15–20 C to solidify the gelatin. The hearts were fixed by perfusion of the right atrium with 40% formalin at 20–30 cm H_2O pressure and suspension of the specimen in the fixative for 24 hours. Absolute alcohol was used for 48 hours to harden the specimen and allow approximately 1.5 cm "breadloaf" sectioning of the heart. High resolution roentgenograms were made of these thick sections using 300 mA for 1–2 seconds at 25–30 KeV on Kodak-M film. Appropriate samples were then processed and sectioned at 4 μ using hematoxylin and eosin, Movat, and PTAH stains for histologic examination.

Results

Patient Group

The data in the eight patients is summarized and shown in Table 1. In four patients (J.B., A.W., C.B., J.H.), the heart was observed at surgery. The surface coronary arteries were intact; the myocardium was tense, adynamic, and somewhat dilated in the area of injury with normal myocardium interspersed with scarring (Fig. 1). On ventriculotomy through the area of injury, the myocardium was noted to be thick, gritty, and the endocardial surface was trabeculated.

Electrocardiograms in all of the patients were abnormal. Elevation of S-T segment was found in seven and abnormal Q waves were present in seven patients.

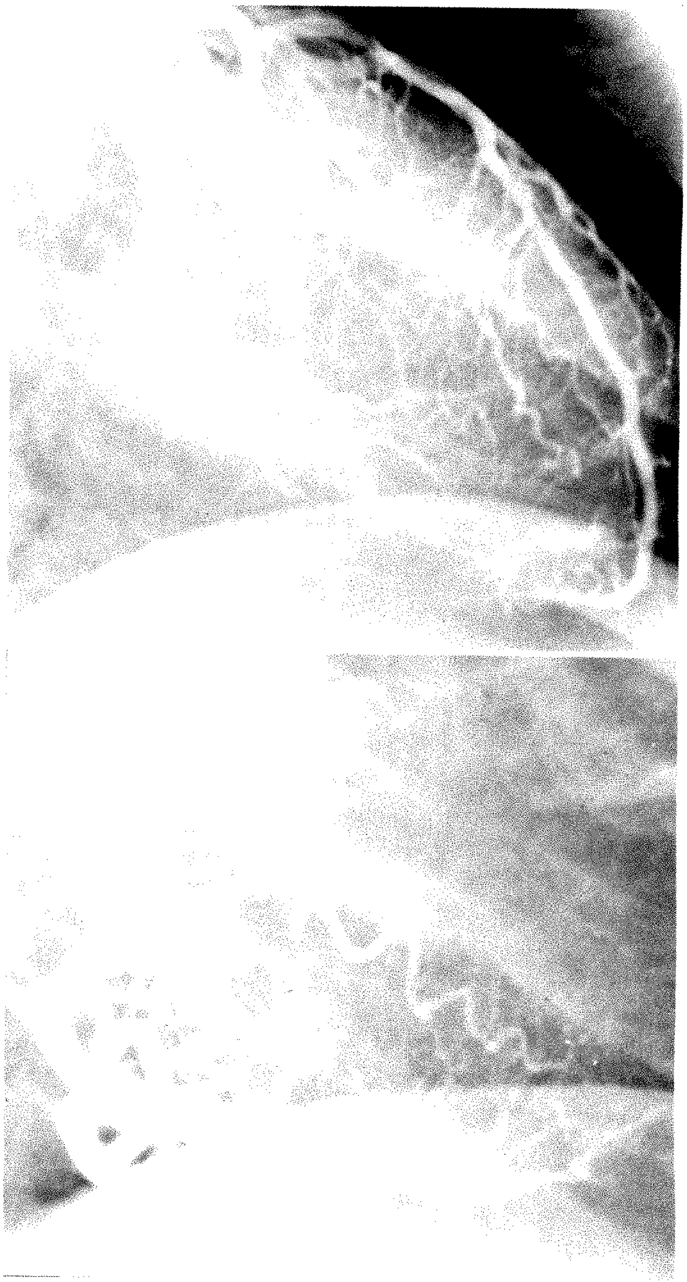


FIG. 2. Coronary arteriogram; patient M.W. in right anterior oblique position 4 weeks after injury. Selective injection into the left coronary artery shown above and right coronary artery below. Demonstrates normal vessels following myocardial contusion.

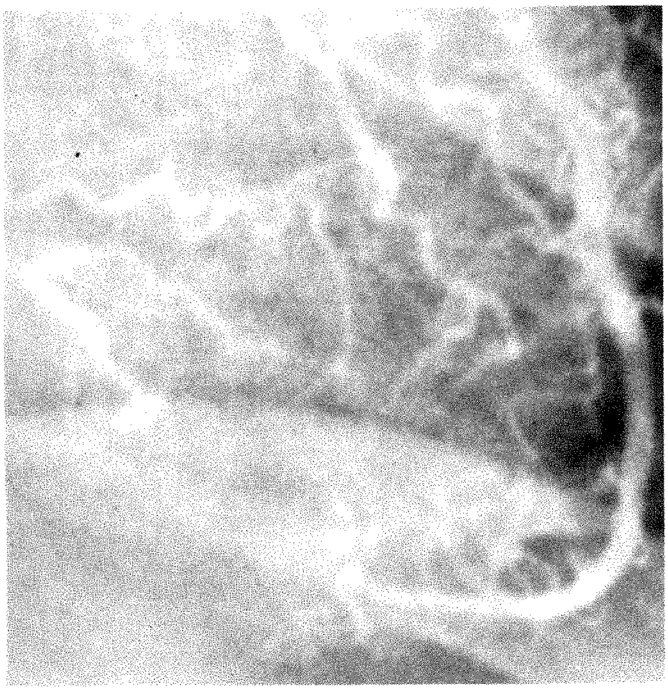


FIG. 3. Left coronary arteriogram, patient M.W. Magnified view details terminal vessels to apex and lateral wall of the left ventricle which appear increased and tortuous, suggesting enhanced circulation to the injured area.

Tachyarrhythmia was the presenting symptom in two patients. One patient had ventricular tachycardia and ventricular fibrillation which required cardiac resuscitation prior to surgical excision of a large area of adynamic myocardium which apparently relieved arrhythmia tendency. Another patient continues to have atrial flutter in spite of cardioversion and medical treatment with digitalis and quinidine.

Four patients had reduced cardiac output and in three of these patients the predominant symptoms were those of congestive cardiac failure. The ventriculograms superimposed in systole and diastole demonstrated akinetic myocardium in five of the eight patients. This area was aneurysmal in four. One patient (J.B.) had a ventricular septal defect due to rupture of the interventricular septum near the apex.

Coronary arteriograms were normal in seven of the eight patients (Fig. 2). In one patient (L.T.) the diagonal branch of left anterior descending was nearly closed. One patient (M.W.) appeared to have increased coronary circulation to the area of injury manifest by increased number of tortuous vessels when studied four weeks after injury (Fig. 3). Histologic examination of damaged myocardium excised in one patient (C.B.) showed many dilated vascular channels among patchy areas of scarred myocardium mixed with normal myocardium (Fig. 8).

Experimental Group

Ventricular arrhythmia occurred immediately after injury in all animals and progressed to irreversible ventricular fibrillation in 12. Nonfatal arrhythmia was most often multifocal, premature ventricular contractions or short periods of ventricular tachycardia. If ventricular fibrillation occurred, resuscitation was impossible.

Cardiac output was reduced immediately after injury. Mean value for cardiac index of 2.49 L/min/M^2 represented 33% reduction compared to mean value in control period prior to injury of 3.69 L/min/M^2. When observed 14–20 days after injury, cardiac output remained low at 2.65 L/min/M^2.

The main coronary arteries were normal in the injected specimens. There was no evidence of thrombosis. The high resolution roentgenograms showed large dilated collections of contrast material in the area of the damaged myocardium and arteriovenous communication immediately after injury (Figs. 4, 5). Small, tortuous vessels appeared 72 hours later. The large collections were initially thought to represent extravasation of contrast media or perhaps artifact dut to pressure injection. Morphologic examination, however, showed these collections were actually dilated vascular channels or giant capillary-sinusoids for lack of a better term (Fig. 6). Extravasation was minimal unless actual laceration of the myocardium occurred. Neovascularity, a

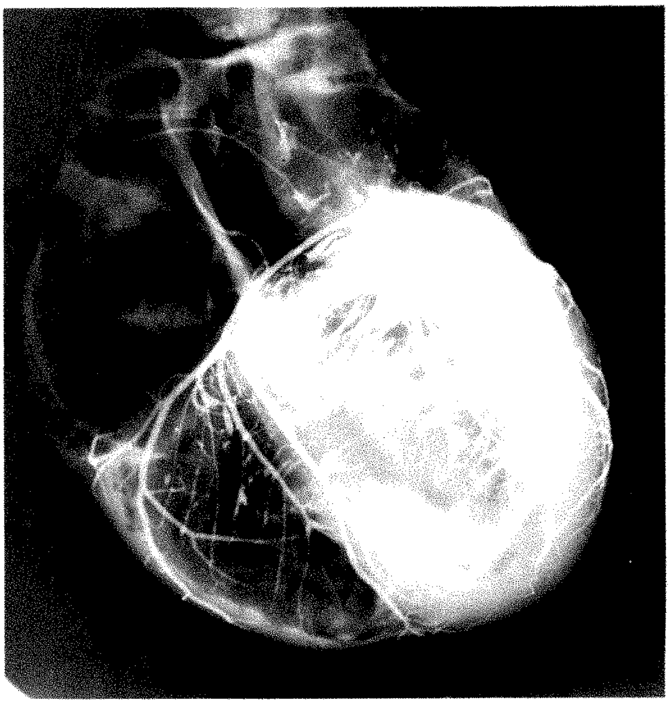


FIG. 4. Coronary arteriogram after myocardial contusion in the dog. Collections of contrast media initially thought to represent extravasation but shown to be in dilated vascular channels (sinusoids).

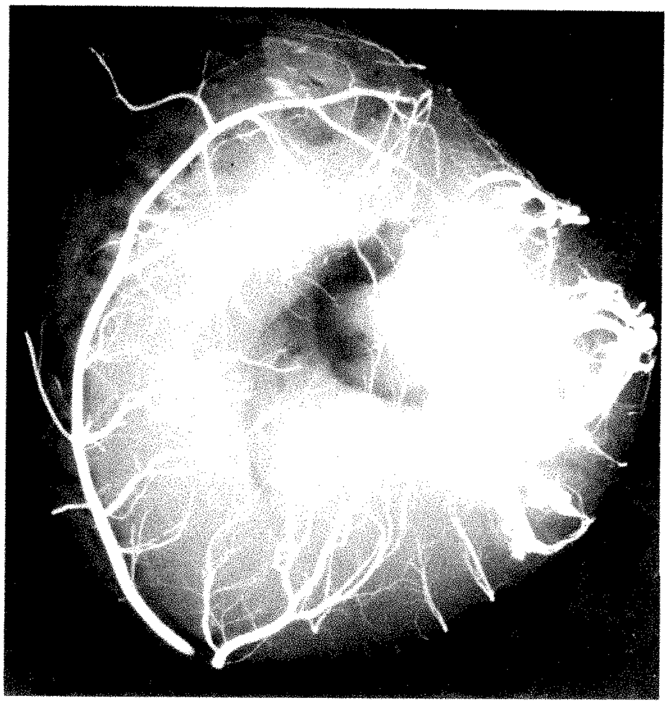


FIG. 5. Coronary artery injection after myocardial contusion in the dog. High resolution roentgenogram of thick section of the heart shows main coronary arteries intact, dilated vascular channels, and arteriovenous filling.

second type of histologic vascular pattern, appeared within 72 hours after injury (Fig. 7). These small, "new" vessels were found in typical granulation tissue as part of the process of repair. The dilated vascular channels persisted in myocardium examined seven days after injury.

Radionuclide Imaging

The scintiphoto following injection of ^{99m}Tc-Sn-polyphosphate in a dog studied one hour after injury showed an obvious area of increased tracer uptake in the area occupied by the heart. A scintiphoto obtained 24 hours after injury in patient M.W. also showed increased uptake in the area of the heart. Serum enzymes at that time were CPK 1280 U, SGOT 750 U, and LDH 1200 U, but the EKG showed only sinus tachycardia.

Discussion

A large proportion of the moderate to severe injuries of the heart area probably overlooked because there may be few signs or symptoms of cardiovascular disorder on the initial examination of the patient. Lasky and associates[14] have shown that moderate-speed impact to a driver in a frontal or left-side collision warrants careful serial examination of the cardiovascular system, particularly if chest contact was made with some structure. It is interesting to note the automobile collision speed was only 20–35 mph in the five cases of myocardial contusion reported in the series. It is well known that extensive cardiac contusion may occur without external evidence of chest injury.[21,26]

Cardiac arrhythmia is one of the most frequent signs

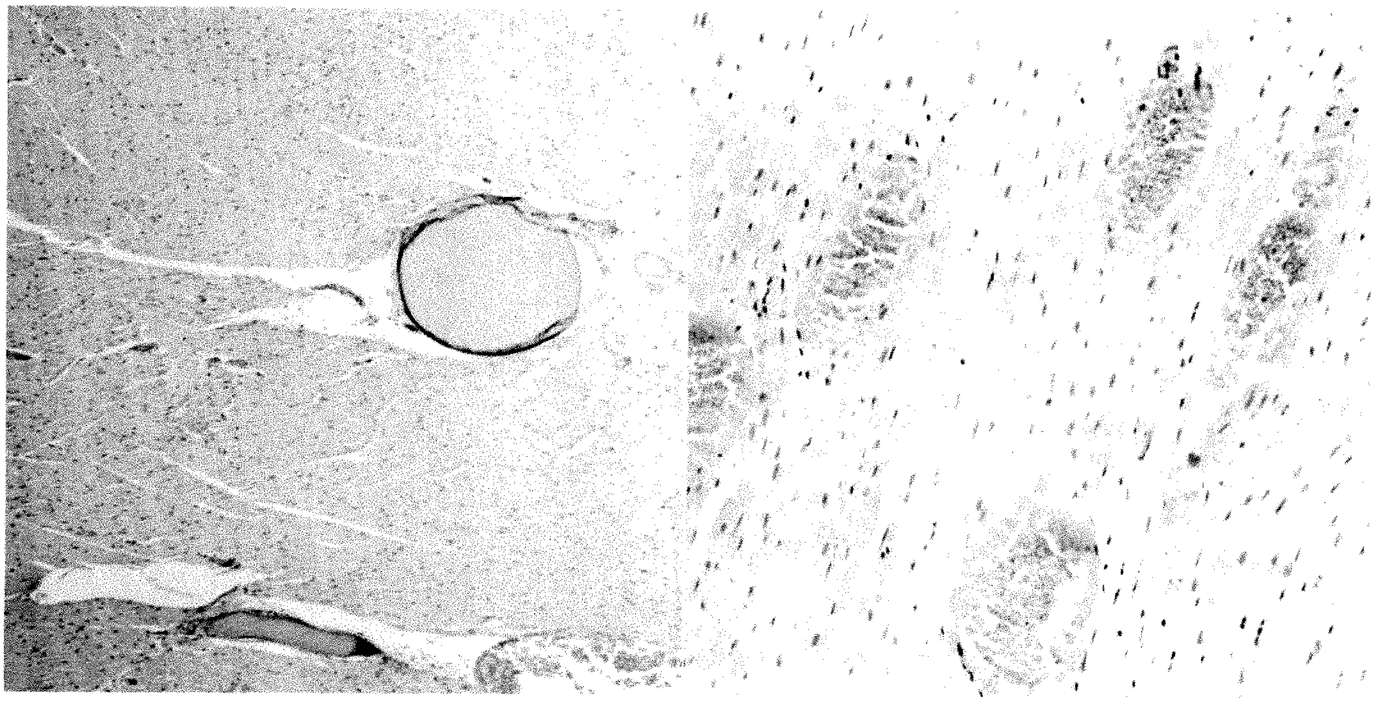


FIG. 6. Myocardial contusion 24 hours after injury in the dog. Photomicrograph (× 40) on left shows contrast media in dilated vascular channels. Higher magnification (× 100) on the right demonstrates blood filled sinusoids.

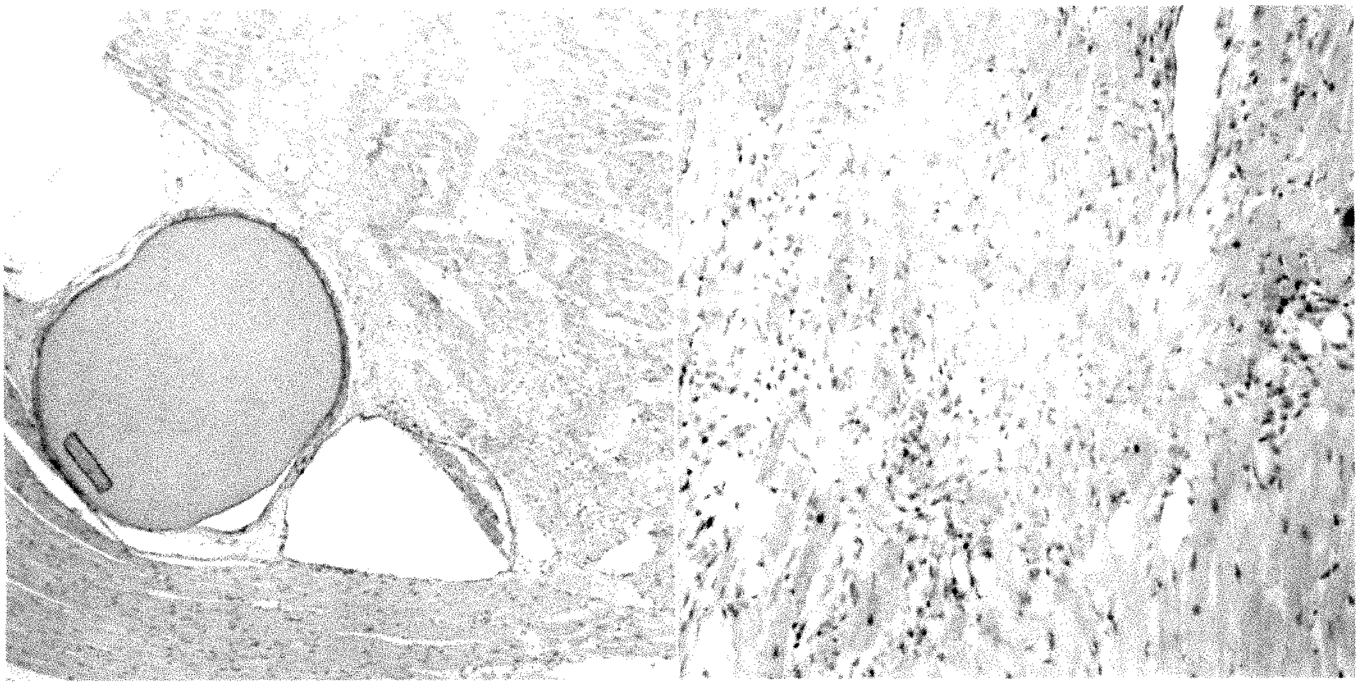


FIG. 7. Myocardial contusion 72 hours after injury in the dog. Photomicrograph (× 40) on left shows dilated vascular channels. An adjacent area (× 100) shows neovascularity (new blood vessels of granulation tissue).

of myocardial contusion. In man, the most common arrhythmia is atrial flutter or fibrillation, as was the case in our patient, D.B. Other studies[7] have confirmed the high incidence of supraventricular arrhythmia and also have shown that ventricular arrhythmia is frequently observed following myocardial contusion as in our patient, C.B. In the experimental animal, ventricular arrhythmia was clearly the most important rhythm disturbance.[13,19,23] When ventricular fibrillation occurred in the experimental setting, it was irreversible. Bright and Beck[5] noted in their early experiments in dogs that the heart did not recover its normal rhythm after it began to fibrillate and death occurred.

There is a suggestion that the location of the myocardial injury may determine the type of cardiac arrhythmia. Moseley, Vernick, and Doty[20] reported conduction defects and reduction of heart rate in sinus rhythm following blunt chest injury when the injury force was applied to the right side of the chest, presumably affecting the right atrium and conduction system. This is in contrast to predominantly ventricular rhythm disturbances in this study when the injury force was to the left side of the chest over the ventricular mass.

An interesting phenomenon of cardiac arrhythmia related to cardiac trauma is that of cardiac concussion or commotio cordis.[11,18] This empiric descriptive term has been used to indicate forces which may not be of great magnitude when applied to the chest, but are of sufficient magnitude to produce sudden jarring of the heart[21] without significant lesion of the myocardium. Cardiac standstill or ventricular arrhythmia may result from intense vagosympathetic response or direct interference with the neuromuscular mechanisms of the heart. The vagal stimulation theory is supported by evidence that atropine prevented slowing of cardiac rate following closed chest trauma in dogs.[20] This phenomenon occasionally finds useful purpose in cardiac resuscitation as the "precordial thump."[27] Presumably, such a blow generates electrical stimulus in a heart that is reactive and may restore heart beat in cases of ventricular asystole due to block or reverse ventricular tachycardia or fibrillation of recent onset.

Reduced cardiac output is the physiologic result of significant myocardial contusion as shown in four of the eight patients in this series. Pomerantz and associates[22] noted 50% reduction of cardiac output measured by impedance cardiography in 11 of 17 patients suspected of having myocardial contusion. Experimentally, the dogs studied in this series had 33% reduction in cardiac output which is similar in magnitude to the previous observations of Moseley, Vernick and Doty[20] in experimental closed chest trauma. In monkeys, Beckman and Friedman[1] found the cardiac output lowered by 40%.

In spite of significant reduction in cardiac output, it is apparent that in the series and in the experience of others, nonpenetrating cardiac trauma is not usually

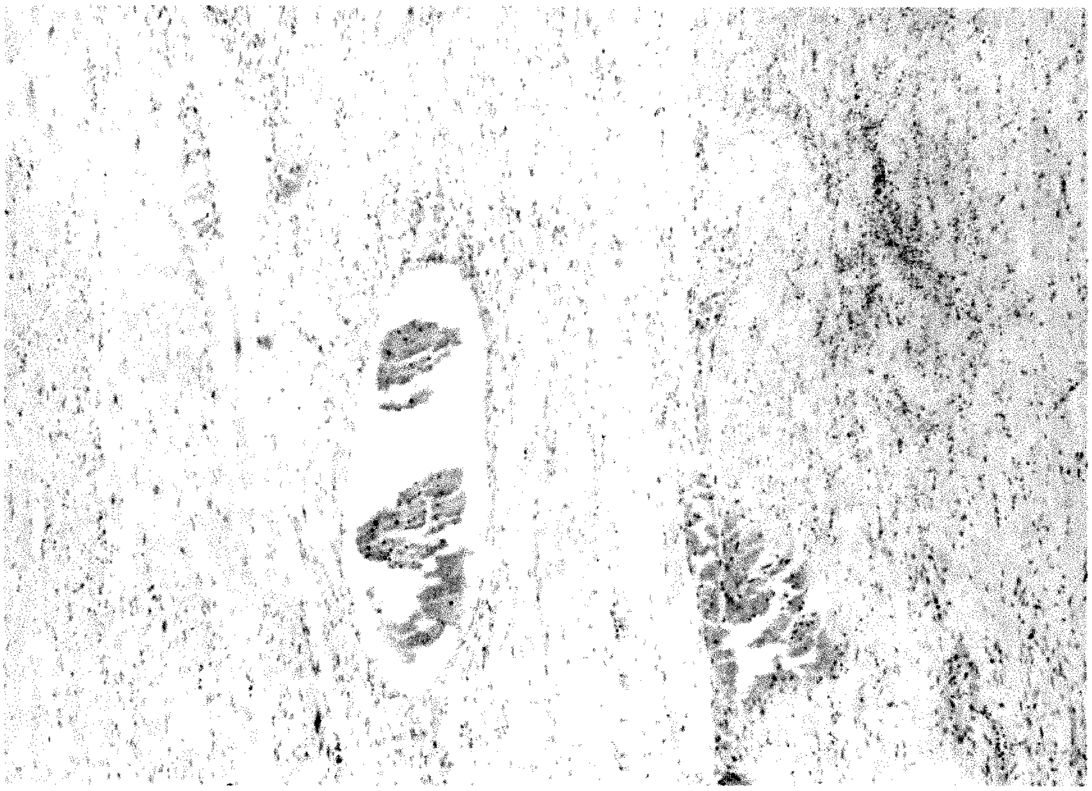


FIG. 8. Section of myocardium excised from ventricular aneurysm 36 months after injury in patient CB. Photomicrograph (× 40) shows dilated blood vessels adjacent to area of myocardial scarring similar to that seen in the experimental preparation.

fatal unless irreversible arrhythmia develops or the myocardium is ruptured.[21] Perhaps this is due to the fact that the injured area remains nourished by a normal or perhaps enhanced blood supply. Even though the extent and distribution of sarcomere damage due to cardiac contusion are similar and often indistinguishable from ischemia myocardial infarction due to coronary arterial occlusive disease, the process of repair is evidently different. Coronary arterial spasm has been refuted by the studies of Louhimo.[16] Parmely[21] found no case of coronary artery thrombosis in a large autopsy series and in this series of patients, all of whom lived, the coronary arteries were normal in seven of the eight. Only one patient had a coronary stenosis due to nonpenetrating missile wound. This patient is probably similar to one reported by Moritz[18] in whom an organized coronary artery thrombosis was found adjacent to a missile tract.

Tortuous or "new" capillary vessels are demonstrated in the patient M.W., suggesting enhanced circulation to the area of injury. High resolution angiograms in the animal studies confirmed patency of coronary arteries and showed similar tortuous vessels and dilated vascular channels in the area of injury. Histologic sections confirmed the presence of contrast media in vascular channels and "new" vessels in areas of repair of cardiac injury. The giant capillary-sinusoid vessels are similar to the dilated collateral vessels in response to the stimulus of cardiac hypoxia described in the review of circulation to the myocardium by Mautz.[17] Blumgart and associates[3] found the normal intercoronary arterial anastomosis in the dog to be slightly larger than those in the normal human heart. Large, thin-walled vascular spaces have been described in experimental and human myocardial contusion by Moritz and Atkins[19] and by Parmley.[21] Patient C.B. in this series had dilated blood vessels in the resected adynamic myocardium. Symbas[28] showed a postmortem coronary arteriogram with "extravasation" of radiopaque material which is strikingly similar to the arteriogram shown in Figure 4 which was initially thought to be extravasation but histologically shown to be dilated vascular channels. It is postulated that the peculiar healing of myocardial contusion with patchy scar interspersed with normal myocardium resulting in an adynamic zone is the result of injury and repair in the presence of normal or enhanced circulation.

The four patients requiring surgery in this series are unique. Only 14 other cases similar to patient J.B., who had a traumatic ventricular septal defect repaired 21 days after injury, have been reported.[8,25] Three patients (A.W., C.B., J.H.), who had resection of aneurysmal, adynamic areas of injured myocardium, are even more unusual. Pupello[24] reported one case and reviewed two others in whom ventricular aneurysm due to closed chest trauma was removed surgically.

Recent studies of Beckman and Friedman[1] have underscored the difficulty of diagnosis of cardiac contusion using data derived from electrocardiographic and serum enzyme studies. Radionuclide imaging of the injured myocardium using ^{99m}Tc-Sn polyphosphate appears to offer promise of obtaining more accurate diagnosis even in mild myocardial contusion as in patient M.W. These preliminary studies are currently being amplified and will be the subject of a future report.[10] The usefulness of this tracer substance in demonstrating myocardium damaged by ischemic infarction has been shown by Bonte and associates.[4] The mechanism is probably calcium accumulation within crystalline hydroxyapatite in the damaged sarcomere being imaged by the apatite labelling polyphosphate tracer substance. This simple, noninvasive test may be helpful in establishing the diagnosis of myocardial contusion in patients with chest trauma.

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Discussion

Dr. John L. Ochsner (New Orleans): Any patient with an acute myocardial injury secondary to blunt trauma deserves to be followed for a prolonged period. We have had two patients who required vigorous treatment of their myocardial injury in the early stages, and then a year later developed progressive aortic insufficiency, and eventually required valve replacement.

(Slide) This was a patient who developed many APC's as you can see, and required intravenous quinidine to control it.

(Slide) The next patient showed evidence of diffuse epicardial injury, as noted with the elevated ST segments across. Followup on both these patients showed aortic insufficiency developing one year later. One required aortic valve replacement; and in the other patient aortic insufficiency as well as a sinus rupture with a false aneurysm posteriorly in the left coronary sinus necessitated aortic valve replacement and obliteration of the aneurysm.

Both these patients' valves showed myxomatous changes, and the right coronary cusp was split, one of into the commissure between the right and the left, and the other one straight down the middle of the right commissure.

I would like to emphasize that after we have treated these patients through the initial stage, it behooves us to follow them very carefully for the complications that may develop, not only within the myocardium, but within the valve structures themselves.

Dr. B. Eiseman (Denver): As Dr. Doty noted, Dr. Pomerantz and I have been using impedance plethysmography to measure depressed cardiac output following trauma for several years. My comments are to emphasize our conclusions and practical clinical implications.

First: There is unexpected myocardial contusion associated with many patients with severe upper abdominal trauma. Typically, this occurs with massive liver, splenic or renal injury, and primary attention is focussed on the abdomen. Usually large volumes of blood are required for resuscitation. An occasional such patient goes into unexpected cardiac failure within 1-3 days following injury when no thought had been given to the possibility of cardiac contusion. Ordinary measurements of cardiac output and myocardial response to volume replacement are difficult to interpret under these circumstances.

Second: Both EKG and enzyme changes are late and gross manifestations of myocardial contusion. Inappropriate low cardiac output is a much more sensitive hallmark.

Third: The practical therapeutic implication is to monitor C.V.P. and beware overtransfusion in resuscitation in patients with severe upper abdominal or thoracic trauma. Myocardial contusion may alter the cardiac response of a healthy young patient to resemble the heart of an old patient with marginal cardiac reserve.

I believe Dr. Doty and Dr. Ehrenhaft's suggested use of Technetium scan is a far more appealing guide to myocardial contusion in these cases than is our use of impedance plethymography, and I look forward to evaluating their technique in our Trauma unit at the Denver General Hospital.

Dr. Donald B. Doty (Closing discussion): I appreciate the two discussants commenting on our paper and underscoring the problem of followup on these patients and discovering injuries due to contusion later on. As noted from our series, there was one patient who presented with his first symptoms of an injury occurring five years before.

Drs. Pomerantz and Eiseman's paper on cardiac output following severe blunt trauma to the chest and abdomen is a classic, and one of the few human studies available regarding cardiac output after this type of injury. It is remarkable that the degree of reduction of cardiac output is so similar in their patients and our study. We have wondered if patients having severe chest injuries, especially those with flail chest who have respiratory insufficiency or traumatic pulmonary edema, might have compromised left ventricular performance with elevation of the left atrial and pulmonary venous pressure, which could be contributing to the respiratory insufficiency, as well as the direct injury to the lung.

Again I would like to emphasize what we think is the most exciting part of our investigation and that is the radionuclide imaging of these injured areas. This particular radioactive isotope—phosphate complex—images not only injured myocardium due to trauma, but also myocardial infarction, and we think it's a useful agent.

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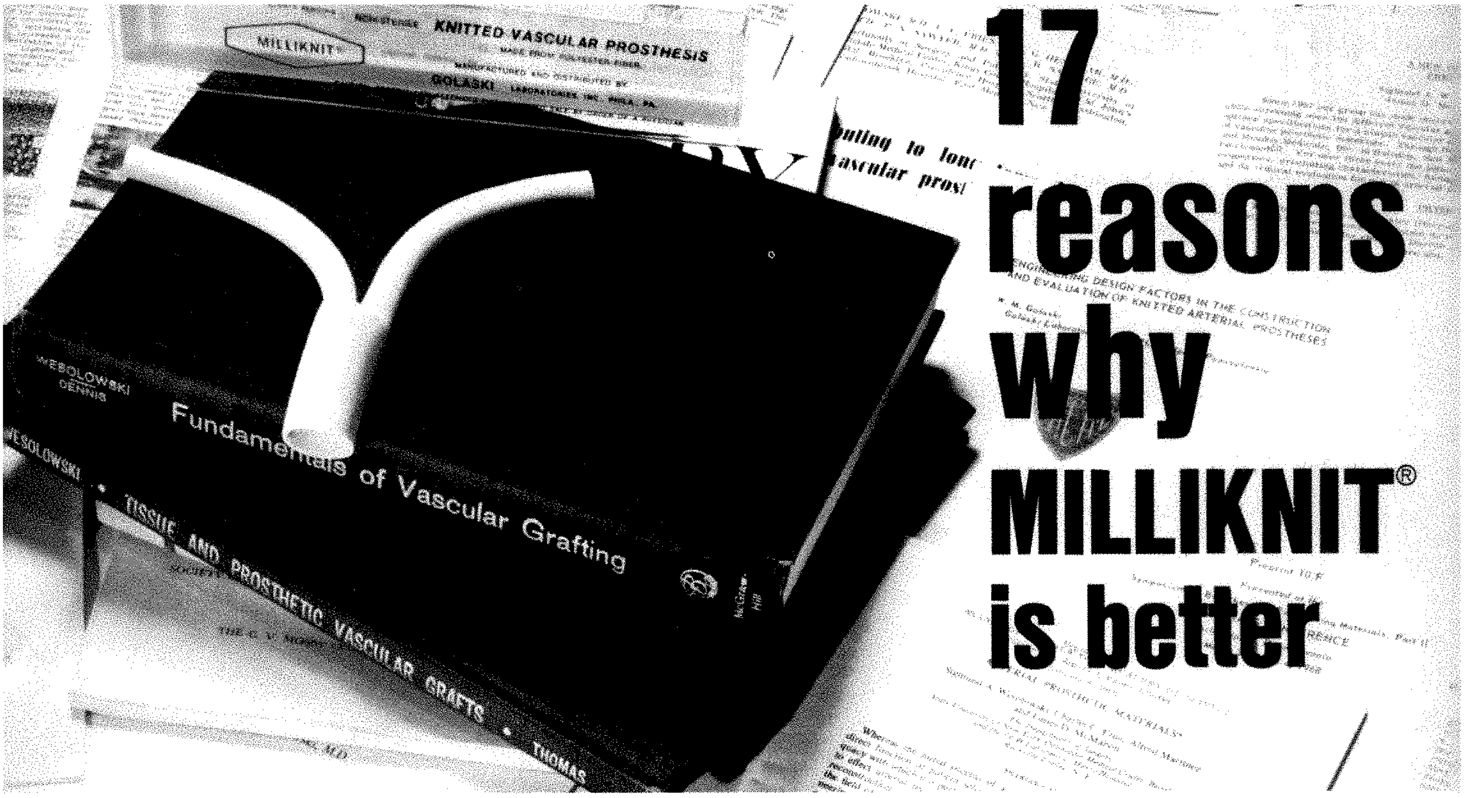
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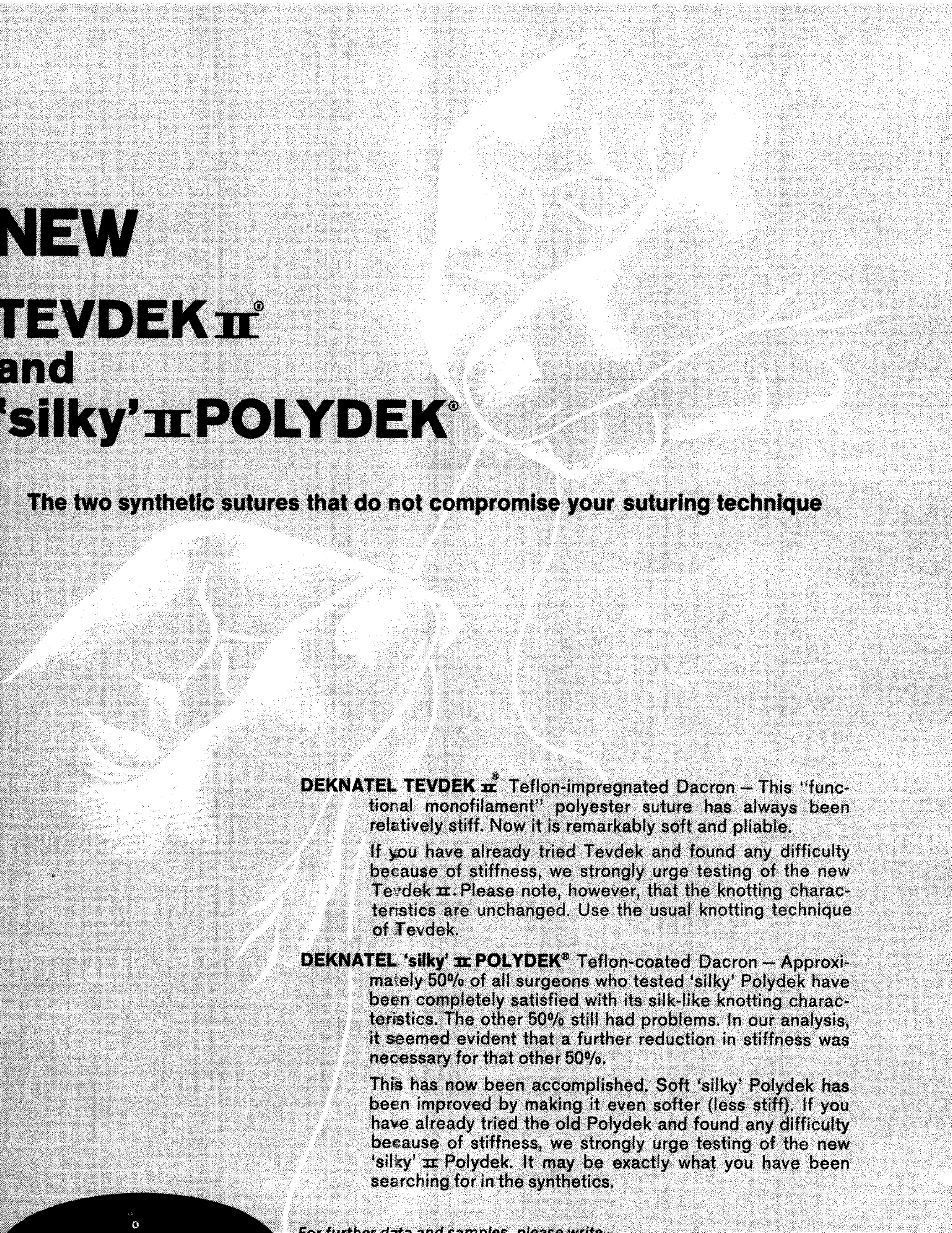

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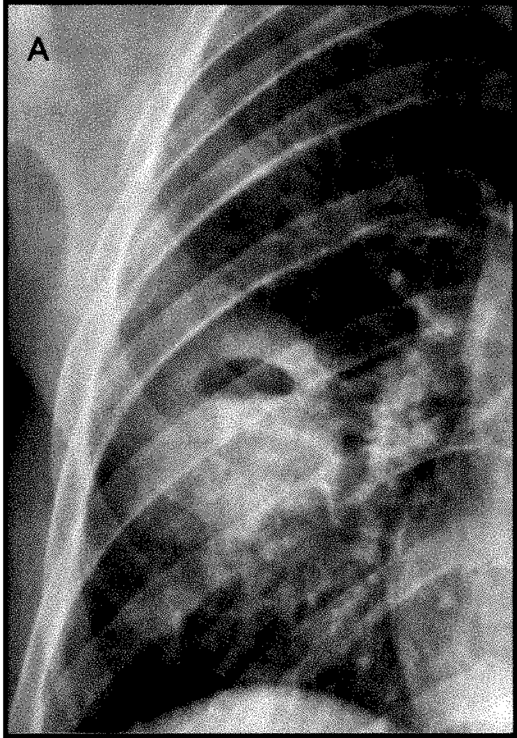

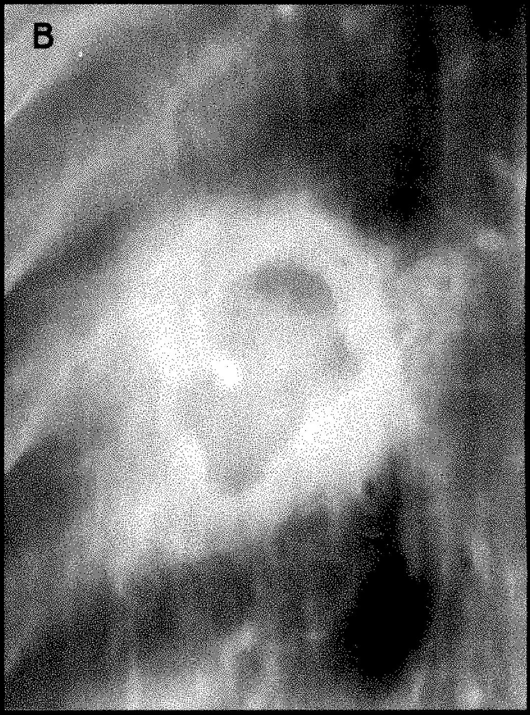

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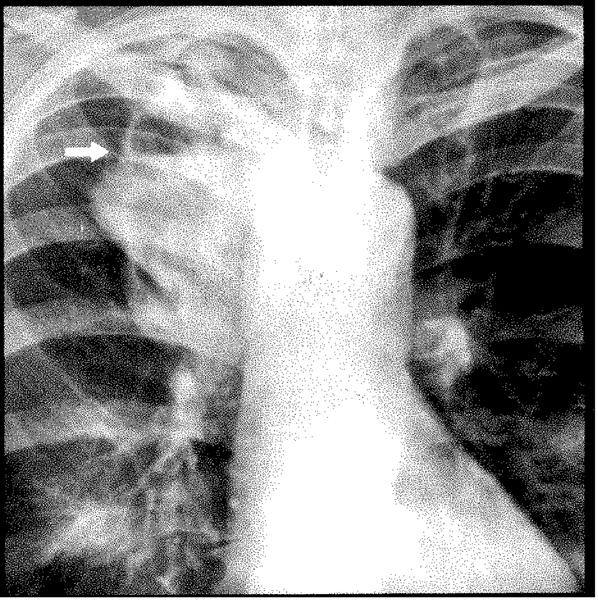

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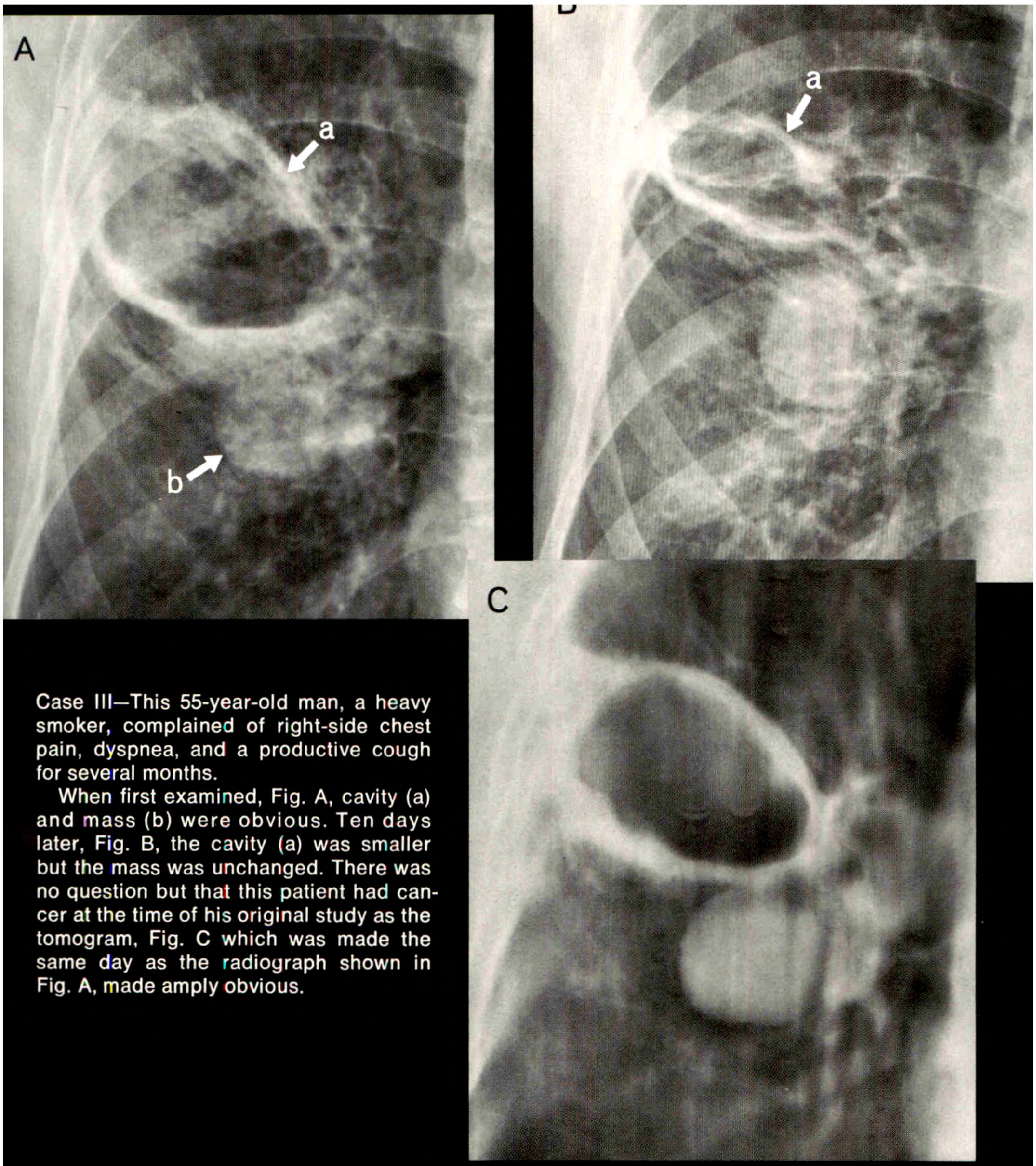

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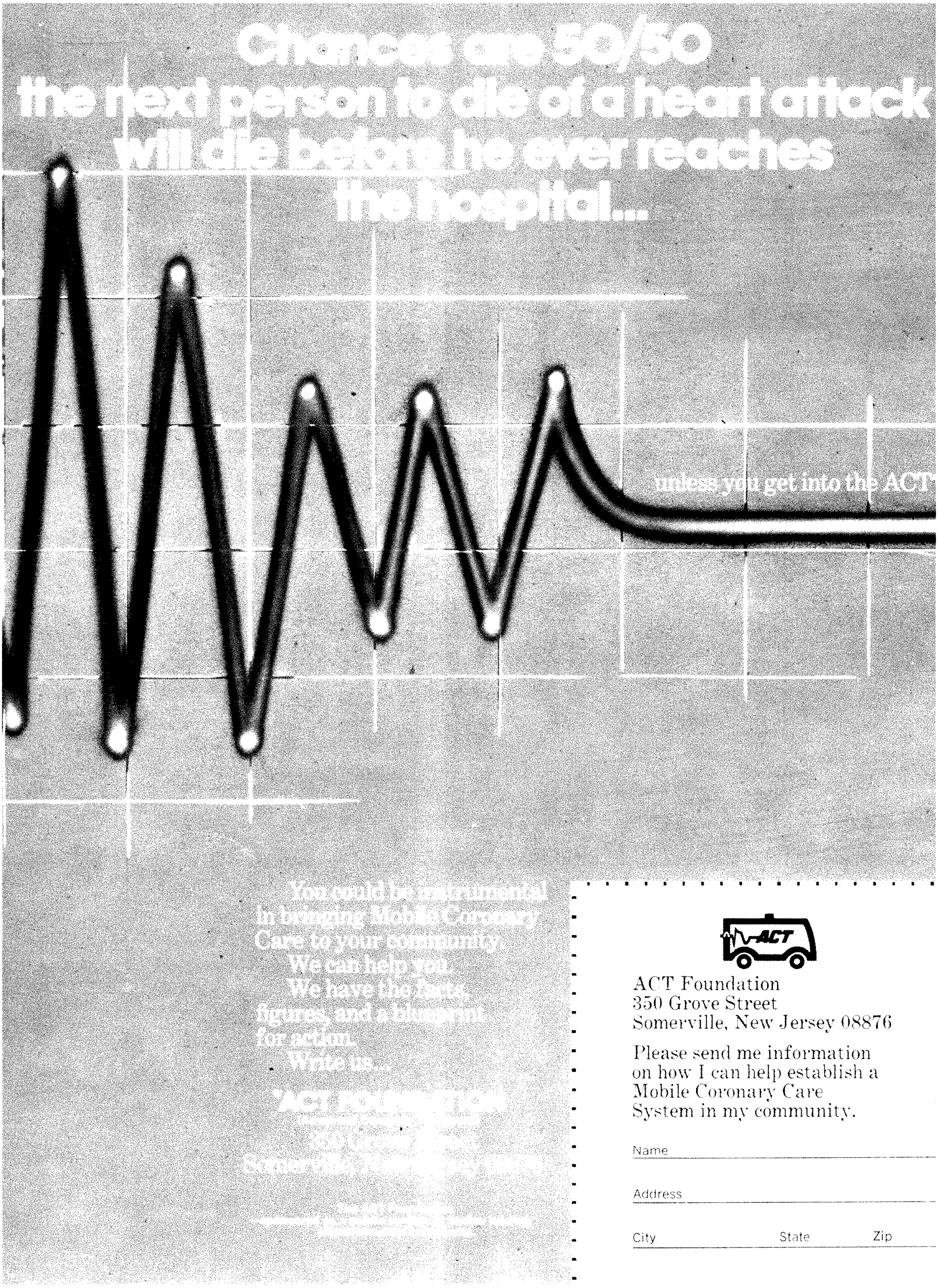

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Transvenous Management of Pulmonary Embolic Disease

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RONALD C. ELKINS, M.D.

Clinical pulmonary embolic disease was categorized into four classes according to hemodynamic and respiratory effects of the occlusion at the time of diagnosis. A new approach to management of massive embolization (Class III and IV) by transvenous catheter embolectomy was attempted in ten patients with initial success in eight. Three additional deaths occurred postoperatively, two from recurrent embolization prior to vena caval plication. In view of this preventable complication, a wire filter device was developed for insertion at the time of embolectomy. The filter has also been utilized in 15 additional patients with lesser degrees of embolization (Class II). The conal shape of the device permits preservation of flow after embolic capture and followup venacavagrams in nine patients up to 20 months postoperative shows patency in all. Complications occurred in both groups related both to the underlying disorder and to the catheter technics.

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THE SPECTRUM of pulmonary embolic disease ranges from asymptomatic patients to those who die rapidly from massive embolization. Treatment of the disorder covers a similar range from anticoagulant or thrombolytic therapy[7] alone to vena caval plication and open embolectomy on cardiopulmonary bypass. One aspect of the problem which has made comparison of results of treatment difficult is a lack of clinical staging of the disorder. To facilitate our assessment we have used the classification shown in Table 1 to categorize patients with a proved diagnosis of pulmonary embolism. In addition, we have attempted to simplify the surgical management of these patients by a transvenous approach under local anesthesia using a catheter technic for pulmonary embolectomy and/or placement of a vena caval filter. Our clinical experience with this approach in 25 patients is the subject of this report.

Clinical Material

The diagnosis of pulmonary embolism was suggested by changes in arterial blood gases and lung scan, and usually confirmed by selective pulmonary arteriography showing filling defects or amputated major vascular branches. The 25 patients studied ranged from 21 to 83 years and included 17 males and seven females. They were classified according to criteria shown in Table 1 based on the observations made when first seen prior to treatment. In general, patients in Class I and II were treated by anticoagulation with heparin to prolong the partial thromboplastin time to twice normal. When this treatment was followed by recurrent embolization or when there was a contraindication to anticoagulation, 15 of the patients became candidates for placement of a vena caval filter. The average age of the patients with this milder degree of embolization was 55 years which did not differ significantly from the average of 52 years in the groups with major embolization.

In ten patients, major vascular emboli were seen on arteriography and an effort was made to capture them within the vacuum-cup catheter for extraction.[6] There were six males and four females in this group ranging from 25 to 79 years and nine were designated as Class IV with shock requiring vasopressor treatment. The remaining patient responded favorably to initial resuscitation but developed gastrointestinal hemorrhage 36 hours later and was found to have pulmonary hypertension at

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TABLE 1. *Classification of Clinical Pulmonary Embolic Disease*

Class	Symptoms	Hemodynamics	Gases	PA Occlusion
I	None	—	—	Focal < 20%
II	Hyperventilation	HR↑	$PaCO_2\downarrow$	Regional 20–30%
III	Dyspnea, Collapse	CVP↑, $\overline{PA}$> 20 mm Hg	$PaO_2\downarrow$ $PaCO_2\downarrow$	30–50%
IV	Dyspnea, Shock	CVP↑, $\overline{PA}$> 30 mm Hg Systemic Pressure↓	$PaO_2\downarrow\downarrow PaCO_2\uparrow\downarrow$	> 50%

right heart catheterization with sufficient embolic occlusion for designation as a Class III. Pulmonary arterial pressures and arterial blood gases and pH were measured in each patient before and after embolectomy. Pulmonary arteriograms usually were performed immediately postoperative and serial lung scans were used for followup evaluation of pulmonary perfusion. Patients who had placement of the vena caval filter alone were evaluated for caval patency at three and six month intervals by venacavagram.

Surgical Technique

Following confirmation of the diagnosis by pulmonary arteriogram, one common femoral vein was exposed for a distance of 4–6 cm under local anesthesia. Braided tapes were passed around the main vessel and its branches for control of blood flow. In two patients where thrombus material could be identified within the vein, care was taken to minimize manipulation of the vein and Fogarty catheters were used for thrombectomy. In most patients, a 2 cm venotomy disclosed no signs of thrombotic material and the vacuum cup catheter or filter carrier was introduced without difficulty. In patients with pelvic disease or extremity edema involving the thigh, contrast media was injected in the femoral vein prior to passage of the catheter through the iliac vein. No evidence of major thrombi prohibiting passage of the catheter was seen in any patient.

After the vacuum-cup catheter was directed into the pulmonary artery, it was manipulated into the branches showing major filling defects or total occlusion. Inflation of the distal balloon permitted isolation of the vascular segment and better visualization of proximity to the embolus by injection of contrast media. Syringe vacuum then was used to capture the embolus within the cup and hold it during catheter withdrawal for extraction as described previously.[6] In one recent case, directional control was added to permit access to more pulmonary arterial branches and it was not necessary to use a balloon to isolate the vascular segment. Following embolectomy in the latter patient, the vena caval filter was inserted by catheter through the same femoral venotomy. Use of contrast media during the embolectomy provided good visualization of the kidneys under fluoroscopy and permitted placement of the filter at a level just below the entrance of the renal veins. Directional control has also been added to the filter carrier catheter and a catheter has been developed to permit insertion by the superior approach through the jugular vein.*

TABLE 2. *Predisposing Factors in the Patients with Major Pulmonary Embolism (Group III & IV)*

Predisposing Factor	No. of Pts.	
Recent surgery		6
Orthopedic procedure	3	
Gastric procedure	1	
Prostatectomy	1	
Drainage perineal abscess	1	
Deep venous thrombosis		5
Systemic hypertension		4
Congestive heart failure		1
Previous above-knee amputation		1

In most patients heparin administration was resumed immediately postoperative and subsequent anticoagulation maintained by warfarin derivatives for periods of three to six months. Elastic stocking support was maintained on the operated limb during the period of hospitalization. Postoperative ventilatory support with a positive-pressure volume cycled respirator was utilized if the PaO_2 was not maintained above 65 mm Hg.

Results

Eight of the ten patients in Class III or IV in whom the diagnosis of massive pulmonary embolism was confirmed by selective pulmonary arteriography survived the catheter embolectomy procedure. The operative mortalities occurred in a 69-year-old female with a five-day history of emboli and a 79-year-old female who arrested at the time of pulmonary arteriography. Efforts to extract multiple lobar pulmonary emboli in the first patient were unsuccessful and she died during preparations for embolectomy on cardiopulmonary bypass. The second patient was supported on partial bypass during extraction of one thrombus but never regained central nervous system function and after further deterioration had ventricular perforation by the catheter as a terminal event.

Following initial favorable response to catheter embolectomy, three additional patients died. One developed

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TABLE 3. *Hemodynamic and Respiratory Response to Catheter Embolectomy in Groups III & IV*

Pt.	Age	Sex	Heart Rate Pre	Heart Rate Post	Embolectomy†	Systemic Pressure Pre	Systemic Pressure Post	Pulmonary Artery Pressure (Mean) Pre	Pulmonary Artery Pressure (Mean) Post	Arterial PO_2 mm Hg Pre	Arterial PO_2 mm Hg Post	Arterial PCO_2 mm Hg Pre	Arterial PCO_2 mm Hg Post	Arterial pH Pre	Arterial pH Post	Outcome
1	32	M	120	130	++	130/90	130/90	51/14 (31)	35/12 (27)	50	64	25	28	7.43	7.50	L & W
2	25	F	92	90	++	80/0*	95/50	30/15 (24)	28/10 (20)	61	95	26	30	7.39	7.44	L & W
3	51	M	150	120	++	150/110*	160/120	55/20 (30)	40/12 (21)	50	107	35	30	7.43	7.45	L & W
4	51	M	100	96	+	144/90	144/90	55/26 (32)	28/16 (20)	41	55	45	43	7.45	7.45	L & W
5	55	M	132	120	+++	100/70*	120/70	60/28 (37)	50/28 (32)	50	70	40	46	7.34	7.45	Died 1 mo.
6	52	M	150	130	++	60/40*	180/60	60/22 (37)	21/19 (28)	40	70	23	31	7.26	7.43	Died 6 hrs.†
7	69	F	110	120	0	80/0*	70/0*	45/30 (34)	45/30 (34)	50	—	29	—	7.48	—	Died
8	54	F	130	130	++	70/0*	100/60	42/20 (28)	30/15 (20)	64	104	37	42	7.31	7.34	Died 4 hrs.‡
9	56	M	110	100	+	90/0*	110/60	35/20 (28)	30/16 (21)	58	70	20	20	7.30	7.40	L & W
10	79	F	128	—	+	64/0*	—	50/22 (30)	—	40	—	24	—	7.25	—	Died

* Vasopressor used.
† Embolectomy: 0—no removal or fragmentation
1—4+ Proportional volume of thrombus removed
‡ Recurrent embolization.

gram-negative pneumonia and empyema, and died in septic shock one month following the catheter embolectomy. The other two deaths resulted from early recurrent embolization and should be considered preventable. In one patient, massive re-embolization occurred at the time of laparotomy for placement of a vena caval clip. The remaining patient died from recurrent embolization four hours after embolectomy before operative placement of a vena caval clip could be performed. Operative vena caval plication or extracaval prosthetic clip placement was performed in four of five surviving patients and a recent patient had additional transvenous placement of the wire filter device.

Predisposing factors usually associated with massive pulmonary embolism were noted in all but two patients (Table 2). These included recent surgery in six patients, deep venous thrombosis in five patients, and systemic hypertension in four patients.

At the time of cardiac catheterization, all but one of the patients required vasopressor and inotropic drugs to maintain systemic arterial pressure and were hypoxemic on oxygen by mask or nasal prongs (Table 3). All but one showed characteristic hyperventilation and decreased $PaCO_2$. Respiratory alkalosis, however, was not seen due to the circulatory shock state and development of metabolic acidosis. The electrocardiogram usually showed non-specific ST and T wave changes although four patients developed right bundle-branch block.

The volume of thrombus removed varied from a few fragments less than 1 cm in length to large firm thromboemboli (Fig. 1). It was not possible to remove all emboli in any patient, but the combination of extraction and fragmentation of remaining emboli improved perfusion on angiography (Fig. 2) and decreased pulmonary arterial pressures (Fig. 3). PaO_2 increased slightly in five of eight patients (Fig. 4) with no change in FIO_2. In the remaining three patients a greater improvement in PaO_2 was observed immediately but was

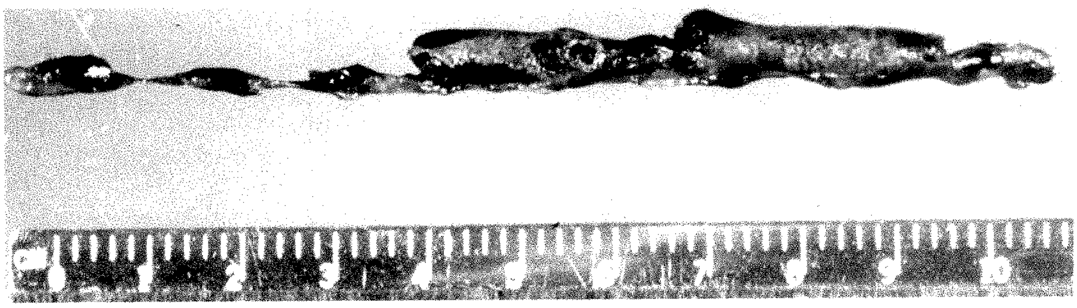

FIG. 1. Pulmonary embolus removed from Patient 5 in a single withdrawal of the embolectomy catheter.

followed within 24 hours by recurrent hypoxemia. The decrease in PA pressures could have been furthered by the blood loss which occurred at the time of embolectomy varying from an estimated 20 to 200 ml. However, no transfusions were required and it was noted that in all but one patient having successful embolectomy, it was possible to discontinue vasopressor therapy immediately postoperative. Retreatment with vasopressors was attempted in the two patients with recurrent embolization who succumbed.

Two patients who were comatose awakened during embolectomy and most patients expressed immediate relief of dyspnea. Postoperative ventilatory support usually was provided by facemask IPPB. Progression to frank pulmonary infarction was noted in three patients but this was not consistently related to the region of restored perfusion. Pleural effusions were observed in two patients and one developed a hemothorax after excessive anticoagulation which responded to thoracostomy tube drainage. Other complications in the surviving patients included pneumonia and empyema in one patient, duodenal stump leakage in a postgastrectomy patient requiring reoperation, and deep venous thrombophlebitis following vena caval plication in one patient (Table 4). Transient ventricular extrasystoles occurred during passage of the catheter through the right ventricle but no episodes of prolonged tachyarrhythmia or fibrillation occurred.

Serial lung scans confirmed restoration of perfusion to the segments from which thromboemboli were removed and showed gradual clearing of the remaining perfusion defects within one to two weeks postoperative. Improved perfusion immediately postoperative in regions where emboli were not removed was felt to result from fragmentation of emboli into more distant branches permitting some restoration of blood flow (Fig. 5). The five long-term survivors ranging from four months to three years postoperative are well and have no recurrence of pulmonary emboli nor signs of chronic respiratory insufficiency.

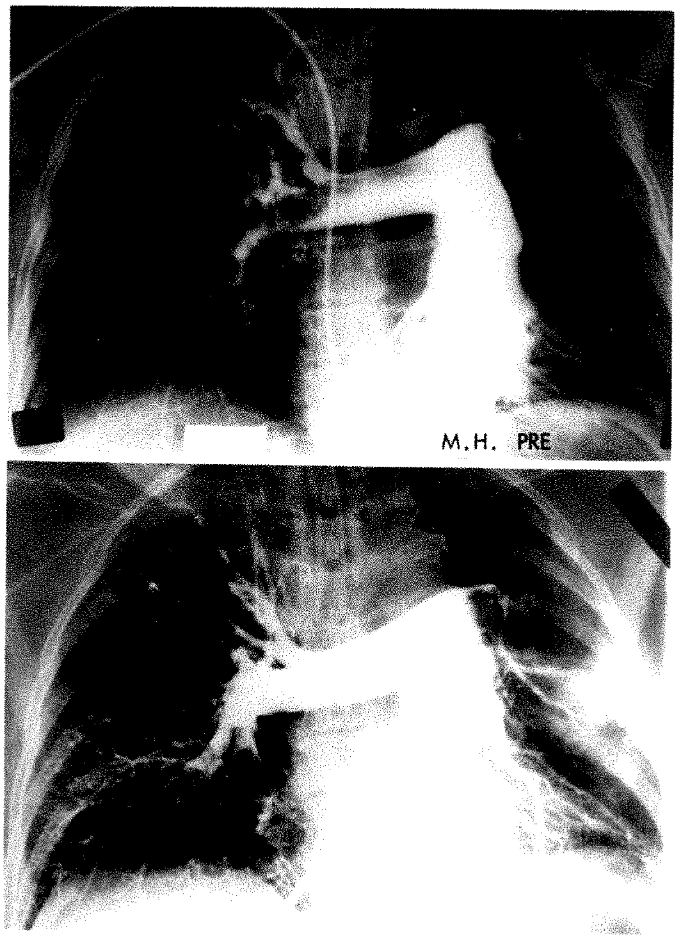

FIG. 2. (Above) Preoperative pulmonary arteriogram obtained in Patient 9 showing virtually complete occlusion of the left main pulmonary artery and a large embolus filling the right main pulmonary artery. (Below) Removal of the embolus on the right improved perfusion on that side and fragmentation during manipulation on the left resulted in some improved perfusion to the left lower lobe.

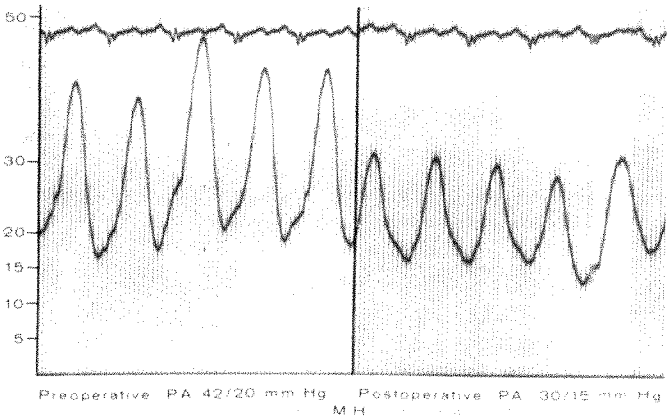

FIG. 3. Phasic pulmonary arterial pressure and electrocardiagram in Patient 9 before (left) and after (right) transvenous pulmonary embolectomy. Systemic arterial pressure had increased as well and it was possible to discontinue vasopressor therapy until recurrent embolization occurred four hour later.

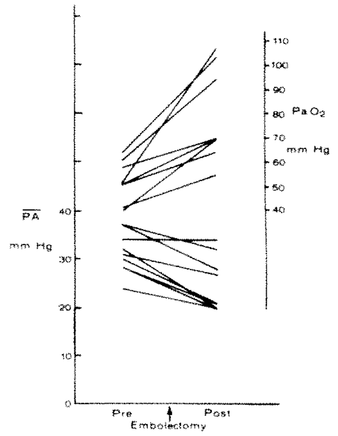

FIG. 4. Changes in mean pulmonary arterial pressure ($\overline{PA}$) following attempted catheter embolectomy (below). In eight of nine patients some improvement in $\overline{PA}$ was observed while a similar increase in PaO_2 (above) was seen in eight patients in whom embolectomy was possible.

TABLE 4. *Complications in Eight Patients Following Embolectomy by Transvenous Catheter Technique*

Complication	No. of Pts.
Pulmonary infarction	3
Pleural effusion or hemothorax	2
Recurrent embolization	2*
Pneumonia and empyema	1*
Duodenal stump leakage	1
Thrombophlebitis	1

* Fatalities.

The occurrence of early re-embolization with death in the two patients following catheter embolectomy prompted development of the filter device for insertion at the time of embolectomy. The combined procedure was used in patient #9 (Tables 3, 5), and filters alone were inserted in 15 additional patients (Table 5). Placement of two filters, one in each iliac vein or iliac vein and vena cava, was necessary in four patients: the first because of lack of fluoroscopy, the second and third because of difficulty crossing the prominence of the pelvic brim, and the fourth because of an anomalous left vena cava which prevented insertion via the right iliac vein. In this latter case, the second filter was placed into the inferior vena cava in an angled position but was observed to be patent at one week on venacavagram. Followup venacavagram at six months, however, showed a trapped thrombus extending above the level of the filter. Because of the potential for recurrent embolization from this extension, she underwent laparotomy and thrombectomy with placement of an external vena caval clip above the level of the filter. Since then she has had one episode of recurrent pulmonary embolization suggested by the presence of chest pain and a new perfusion defect on lung scan. No other patient has had symptoms or signs of recurrent embolization after vena caval filter insertion. Distal thrombophlebitis occurred in two patients and three of the 20 groin incisions developed wound complications requiring open dressing.

There were four deaths in these patients after filter insertion secondary to their primary underlying disease. Two patients with recurrent carcinoma and two patients with underlying heart disease and renal failure died at intervals of 1–8 months postoperative. Examination of the pulmonary vascularity at autopsy in three of them show no evidence of recurrent embolization. One showed thrombosis of one of the filters placed in the iliac vein but no extension of thrombus above that level. Of the 12 remaining patients, nine have undergone postoperative venacavography at intervals of 3–20 months postoperative. All have shown patent vena cavas and none has evidence of obstruction of venous return or any increased lower extremity stasis sequelae (Fig. 6). Five of the patients were maintained on oral anticoagulation postoperatively for varying periods of time and one was maintained on aspirin therapy. Within the limits of their underlying venous disease, all of the surviving patients have returned to their preoperative level of activity.

Discussion

The development of a catheter technique for extraction of pulmonary emboli resulted from a high mortality rate with open embolectomy in our experience, usually secondary to pulmonary hemorrhage following technically satisfactory embolectomy. Other reports also showed low overall survival rates prior to 1970.[1,3] As originally proposed, a double lumen balloon-tipped catheter was used to permit isolation of the pulmonary vascular segment and injection of contrast media for better approximation of the cup device to the embolus.[4] Only emboli in line with the axis of the vessel however could be withdrawn readily. This subtotal embolectomy

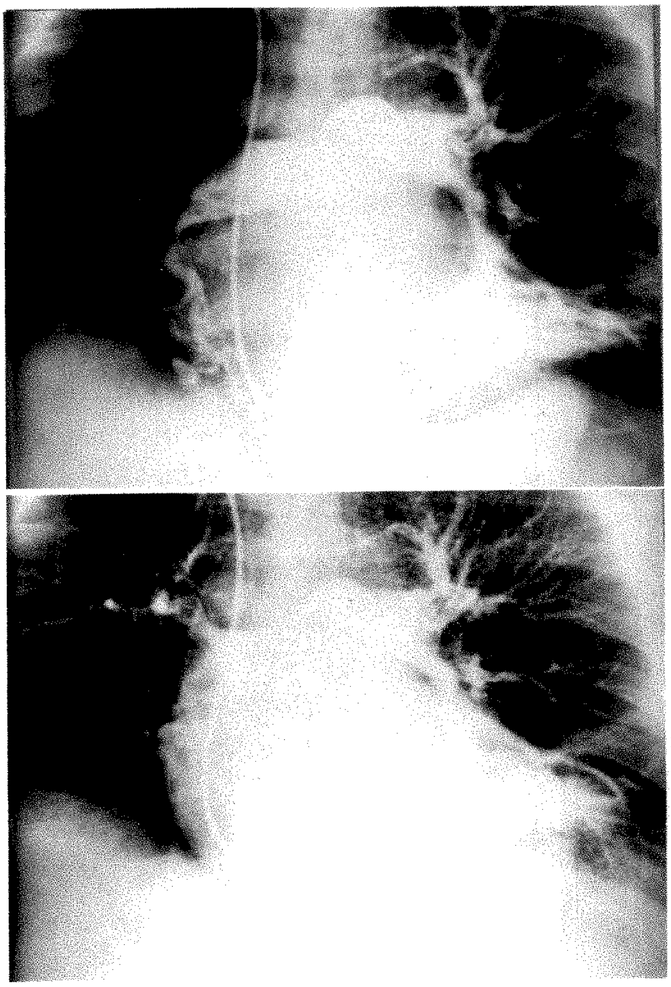

FIG. 5 (Above) Pulmonary arteriogram obtained in Patient 4 showing filling defects and absence of perfusion, primarily on the right. (Below) Repeat pulmonary arteriogram after catheter embolectomy with removal of only a few fragments of old thrombi. Perfusion is noted to be restored to the right upper lobe and additional segments of both lower lobes.

TABLE 5. *Clinical Experience with Transvenous Caval Filter Insertion*

Pt.	Age	Sex	Diagnosis	Filter Locations	Venacavography	Anticoagulation	Results
11	61	M	Thrombophlebitis	Bilateral iliac	Patent (20 mos.)	Warfarin	Recovered
12	21	F	Recurrent phlebitis seizure disorder	Iliac and IVC	Patent (6 mos.)	None	Reoperated-thrombectomy caval clip,? recurrent PE
13	83	M	MI, thrombophlebitis	IVC	Patent (12 mos.)	None	Recovered
14	55	M	Thrombophlebitis	IVC	Patent (12 mos.)	Warfarin	Recorved
15	23	F	Septic thrombophlebitis Post partum	IVC	Patent (12 mos.)	None	Recovered
16	61	M	Thrombophlebitis	IVC	Patent (12 mos.)	Warfarin	Recovered
9*	56	M	Massive P.E. Post op antrectomy	IVC	Patent (10 mos.)	Warfarin	Recovered
17	56	M	Post op coronary bypass	Bilateral iliac	None	None	Died 2 mos postop
18	49	F	Hypernephroma	IVC	None	None	Died of metastases
19	62	M	Post op prostatectomy	Bilateral iliac	Patent (6 mos.)	None	Recovered
20	49	M	Massive P.E., Cardiac arrest, anuria	IVC	None	Heparin	Died
21	70	M	Thrombophlebitis	R. iliac	None	Heparin	Died
22	39	M	Recurrent phlebitis	IVC	Patent (3 mos.)	Warfarin	Improved
23	30	F	Post-cholecystectomy	IVC	None†	None	Resolved
24	49	M	Amputation	IVC	None†	ASA	Resolved
25	63	M	Recurrent phlebitis	IVC	None†	None	Resolved

* See Table 3
† Recent Cases

usually was effective in reducing pulmonary vascular resistance and improving cardiac output.[6] The minimal or transient improvement in blood gases was attributed to the remaining emboli or effects of vasoactive materials released as a result of embolization.

Although the concept appears valid, the results of catheter embolectomy have not improved the survival rate which at 50% is comparable to the collected experience with 306 cardiopulmonary bypass cases through 1971 reported as 51.6% survival rate by Turnier *et al.*[9] Even better results with survival rates greater than 70% have been reported since then with more widespread use of partial cardipulmonary bypass support.[2,8,9] If the concept of a catheter approach to the problem is valid, then the explanation for the failure to improve survival must relate either to the technic of its application or to the gravity of the clinical situation. The latter is certainly a major factor but has not limited the progressive improvement in survival rates reported. It seems likely that at least two additional patients would have survived with the present technique but this experience suggests that efforts must be directed towards further improvement in catheter design and application of this investigational approach.

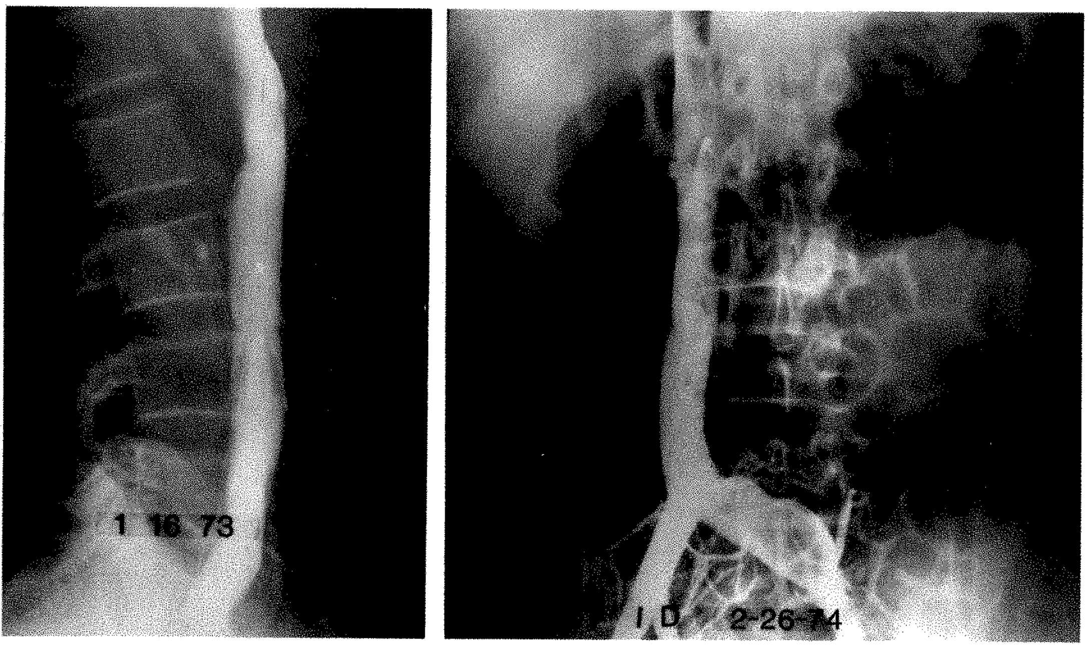

FIG. 6. Venocavagrams obtained in Pt. 14 one week following filter insertion (left) and after one year (right). The vena cava has remained patent with no evidence of collateral formation.

To improve the yield from catheter embolectomy, a catheter has been modified to permit directional control of the cup unit. At the same time, a smaller cup has been used to permit access to more segmental branches. With these modifications, the balloon does not appear necessary for retrieval of emboli. This probably results from better approximation of the cup to the end of the embolus. It is still possible, however, to capture emboli eccentrically with suboptimal seating within the cup. Under these circumstances the embolus may dislodge during passage retrograde through the right heart and require recapture. In one patient (Pt. #6, Table 3) a large embolus became wedged in the iliac vein during attempted removal and this same patient died from recurrent embolization during laparotomy, for placement of a vena caval clip. This experience prompted development of the stainless steel wire filter which could be inserted at the time of embolectomy through the same or opposite femoral venotomy. The availability of this device should prevent the deaths associated with recurrent pulmonary embolism providing immediate protection from the time of embolectomy and obviating the need to transfer the patient to an operating room for general anesthesia and laparotomy. In addition, the cone shape of the unit permits filling of 70% of its depth while reducing cross-sectional area by only 49%.[5] This preservation of blood flow around a trapped embolus has resulted in resorption of the embolus in experimental studies and can avoid the sequelae of vena caval occlusion and venous stasis.

A systematic approach to the patient suspected of having massive pulmonary embolism requires that the diagnosis be confirmed by pulmonary arteriography. The presence of marked hypotension does not obviate the need to define those patients with probable myocardial infarction. If vasopressor agents do not restore adequate perfusion, then consideration should be given to cannulation of the femoral vessels under local anesthesia for partial extracorporeal circulation to permit right heart catheterization and pulmonary angiography. After the diagnosis and location of the emboli are established, the insertion of the vacuum-cup catheter is accomplished via the opposite femoral vein in the catheterization laboratory. Then while an effort is made to extract the emboli, preparations can be made in the operating room for open embolectomy should the catheter procedure prove unsuccessful. At the very least, the vena caval filter can be inserted through the femoral venotomy to prevent further migration of emboli.

For patients in Class II or III who develop complications from anticoagulation or demonstrate recurrent embolization a clear indication exists for insertion of a vena caval filter. In these patients or others who are selected for vena caval plication, an effort could be made to remove the embolus by catheter prior to insertion of a vena caval filter, particularly in patients with poor pulmonary function or underlying heart disease.

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Discussion

Dr. Marion S. DeWeese (Columbia, Missouri): During the past several decades we have experienced cyclic waves of enthusiasm and lack of enthusiasm for open pulmonary embolectomy. The classification which Dr. Greenfield has developed for the evaluation of patients with clinical pulmonary embolic disease should prove helpful in enabling us to avoid some of our past mistakes in patient selection, and should provide helpful objective criteria upon which to base a comparison of therapeutic results as well.

Although similar criteria are being commonly used by many of us, and this classification may be subject to some modification in the future, adherence to the principles which the authors are seeking to firm up should help temper the injudicious and promiscuous use of these techniques, which is always a hazard when new methods are introduced in this field.

We have been personally aware of and have followed the development of these procedures with great interest over the past several years. Although we have had no personal experience with the transvenous suction catheter technique, one must be impressed by the salvage rate which has been achieved in this initial series. The results are equal to, or better than, most of those recorded in which open operations employing cardiopulmonary bypass have been utilized. The greater simplicity and the apparent lower operative risk with the transvenous method are self-evident. The methodology is certainly deserving of wider clinical trial.

The high success rate which the investigators have achieved with the cone-shaped transvenous filter is also commendable. The results of this phase of their study closely parallel our own long-term favorable experience with the transabdominal method of providing caval filtration, and which we presented before this body last year. Again, the potential advantages of the transvenous method are very real.

In closing, I would like to ask Dr. Greenfield if he would be good enough to summarize for us again the potential pitfalls and hazards in applying the technique, particularly the suction catheter one. The one instance of ventricular perforation which he reported is somewhat disarming. A wave of enthusiasm is certain—and rightfully so—to arise across the country for applying these methods, by surgeons and nonsurgeons alike, and especially by those nonsurgeons who are conversant with cardiac catheterization techniques. I have been a little alarmed by the great interest which some cardiologists have shown, in that they seem anxious to perform the procedures themselves. All will need to be alert to the potential complications, and be prepared to deal with them.

Dr. Lazar J. Greenfield (Closing discussion): In terms of problems with the catheter, they obviously are numerous, and we feel that we have not developed the final catheter which will be foolproof.

I think that the likelihood of cardiologists undertaking the procedure is relatively small, if they have to expose the common femoral vein and all of its branches. This approach is not one that will be casually undertaken by anyone and should be reserved for an experienced vascular surgeon.

I should add that we have developed, in addition, a carrier which will permit insertion from the superior approach via the superior vena cava and jugular vein. This will have obvious advantages in some cases.

One question that has come up repeatedly is the potential risk from insertion of catheters and devices from below in patients with thrombotic disease, particularly in patients who have evidence of pelvic or lower extremity thrombotic disease. We have routinely inserted a catheter at the time of venotomy and identified by contrast medium the path that we expected the catheter to take. In no case, however, has there been evidence of thrombi which might be dislodged by the passage of the catheter.

Other problems are numerous and are reviewed in the paper. I think that technical considerations will merit animal experimentation prior to undertaking the procedure in patients, for people who are interested in performing this technique.

Saphenous Vein Aortorenal Bypass Grafts:

Serial Arteriographic Study

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One-hundred and eight autologous saphenous veins were used to construct an aortorenal bypass in 94 patients and were followed from five months to nine years. There were three operative deaths. Twelve grafts thrombosed. In seven patients the thrombosis was demonstrated in the early postoperative period. In the other five patients an early postoperative arteriogram was not done, the thrombosis was first demonstrated arteriographically 4½–9 months following operation. In the latter patients it is impossible to determine when the thrombosis occurred. No graft demonstrated to be patent in the early postoperative period was subsequently found to be thrombosed. Therefore it is likely that almost all thromboses occurred in the immediate postoperative period and were the result of technical errors in the arterial reconstruction. A total of 130 followup arteriograms were done in 75 patients with 89 patent grafts. Long term, serial followup arteriograms were done in 29 patients with 39 vein grafts. Three different patterns were observed: 1) the vein graft maintained its initial size and configuration (62%); 2) the vein graft underwent uniform dilatation throughout its length (20%); and 3) the dilatation progressed to aneurysmal proportions (5%). Significant suture line stenosis developed in one patient who also had recurrent renovascular hypertension. Progression of severity of "apparently insignificant" stenosis or development of a new lesion in the contralateral renal artery was observed in 12 of the 29 patients (41%). These patients serve to emphasize the fact that nephrectomy is ill-advised in patients with renovascular hypertension except under the most demanding circumstances. Finally, there is an urgent need for a careful comparative study of the grafts that are currently being used to construct aortorenal bypasses.

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ALTHOUGH the saphenous vein has been frequently used to replace or bypass arterial lesions over the last 20 years there is very little in the way of factual information regarding the long term performance, durability and patency of these vein grafts. Notable exceptions are the reports of Fry and his associates and of Szilagyi and his associates; as well as, the recent increasing frequency of reports of arteriographic studies of aortocoronary bypass grafts.[1,4,5,7,9,10] The main reason for the paucity of followup data has been a reluctance to perform followup arteriograms in patients who are otherwise doing well. However, the finding of aneurysmal dilatations and stenoses in 16% of 74 aortorenal vein grafts studied 8–109 months following implantation, as reported by Stanley, Fry and Ernst, clearly emphasizes the need for more such studies.[9]

From December 1962 through December 1973, over 1400 consecutive hypertensive patients have been studied at Vanderbilt University Medical Center. In each patient a rapid sequence excretory urogram and a renal arteriogram were done. A diagnosis of renovascular hypertension (RVH) was made in 253 patients and of these 217 had operative treatment prior to 1974. A segment of autologous saphenous vein was used to bypass a renal artery stenosis in 94 patients. In 14 patients bilateral saphenous vein aortorenal grafts were implanted. Thus a total of 108 saphenous vein aortorenal bypass grafts were done. There were three operative deaths. An attempt has been made to obtain followup arteriograms in the surviving patients. This has been accomplished in 75 of the patients in whom 89 saphenous vein grafts have been implanted. A total of 130 followup arteriograms have been done in these 75 patients. A smaller group of 29 patients with 39 vein grafts have had serial long term arteriographic studies 12 to 108 months fol-

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lowing implantation. A total of 72 arteriograms have been done in these 29 patients. Assessment of the fate of the vein grafts provide the basis of this report.

Materials and Methods

Our criteria for selection of patients for operative treatment has been described in detail elsewhere.[6] If the arteriogram shows a renal artery stenosis then renal venous renin assays and split renal function studies were done. If either of the latter two tests were positive a diagnosis of RVH was considered established and operative treatment was usually recommended.

In the 94 patients who underwent vein bypass the etiology of the renal artery stenosis was fibromuscular dysplasia in 41 (32 females and nine males). In six of these latter patients bilateral bypasses were done. Sixty-one vein grafts were used to bypass atherosclerotic renal artery stenosis, bilateral in eight patients. This group includes 25 females and 28 males. Only one patient was less than 20 years of age. The patients ages ranged from 13 to 67 years.

The operative technique was fairly well standardized in all patients. A 5 cm segment of the proximal most portion of the saphenous vein was mobilized, branch veins were ligated and divided. Following removal the vein was gently distended with heparinized saline and constricting adventitial bands excised. Mannitol (25 g) and Heparin (50 mg) were administered intravenously prior to application of occluding clamps on the renal artery. The renal artery anastomosis was done first. In the vast majority of the cases an end to side anastomosis was done. When the renal artery anastomosis was completed, the vascular clamp was removed from the renal artery and a bulldog clamp applied to the vein graft adjacent to the suture line. Thereafter the anastomosis between the graft and the aorta was done. On the right side the vein graft was generally brought retrocaval and on the left behind the renal vein. Of the 108 vein grafts 54 were implanted on the right and 54 on the left. For the past two years magnification and 5.0 or 6.0 Prolene sutures have been used in creating the anastomoses.

Generally, an arteriogram has been done 7–8 days following operation. Thereafter, we have tried to obtain an arteriogram each year. In the early years covered by this report only a flush aortogram was obtained. For the past three years a flush AP aortogram, right posterior oblique flush aortogram and bilateral selective renal arteriograms have been done on almost every patient. During the last six months of 1973 our Department of Radiology did a special study.[2] The question they addressed related to the use of a pressure dressing following retrograde femoral catheter aortography (Table 1). They compared the use of a pressure dressing versus a bandaid following retrograde femoral arteriography in 754 consecutive patients. All patients had a 10–15 minute period of manual compression of the femoral artery puncture site prior to application of the pressure dressing or bandaid. Details of the study will be reported elsewhere.[2] In the pressure dressing group, delayed bleeding occurred in 0.52% while in the bandaid group delayed bleeding occurred in 3.76%. (p. < 0.01). In each patient who bled manual compression was reinstituted and effective hemostasis was obtained. One patient out of 754 had a significant complication, a femoral artery thrombosis which was easily corrected under local anesthesia.

TABLE 1. *Complications of Retrograde Femoral Catheter Aortography: 754 Patients at Vanderbilt University Hospital 1973*

Complications	Pressure Dressing	Bandaid
Significant Groin Hematoma	2/382	2/372
Delayed Bleeding*	2/382	14/372
Femoral Artery Thrombosis	0	1/372 (0.27%)

* Fifteen minutes to eight hours after manual compression.

Results

There were a variety of observations in the followup arteriographic studies, some involved alterations and changes in the 89 vein grafts and in the renal arteries of the 75 patients. These are listed in Table 2. They include: thrombosis of the graft, thrombosis of the vein graft and renal artery, suture line stenosis, maintenance of a normal caliber, uniform dilatation of the graft, aneurysm of the graft, progression of renal artery lesions and the developmental of new renal artery lesions.

Thombosis of the Graft

In five patients the graft thrombosed but the stenotic renal artery remained patent. The cause of the thromboses could not be determined. In two patients the thrombosis was demonstrated in the early postoperative period (7–10 days). In three other patients it was dem-

TABLE 2. *Arteriographic Assessment of Saphenous Vein Aortorenal Grafts*

Graft Configuration	Assessment of Graft	Grafts at Risk*
Thrombosis of graft	5/89	6%
Thrombosis of graft and renal artery	7/89	8%
Suture line stenosis	15/89	17%
Patent and normal graft	24/39	62%
Dilatation of graft	8/39	20%
Aneurysm of graft	2/39	5%
Progression of renal artery lesions	11/29	38%
New renal artery lesions	1/29	3%

* The incidence of thrombosis and stenosis are based on early and/or late arteriographic studies. The incidence of the other changes is based on arteriograms done 12–108 months following operation.

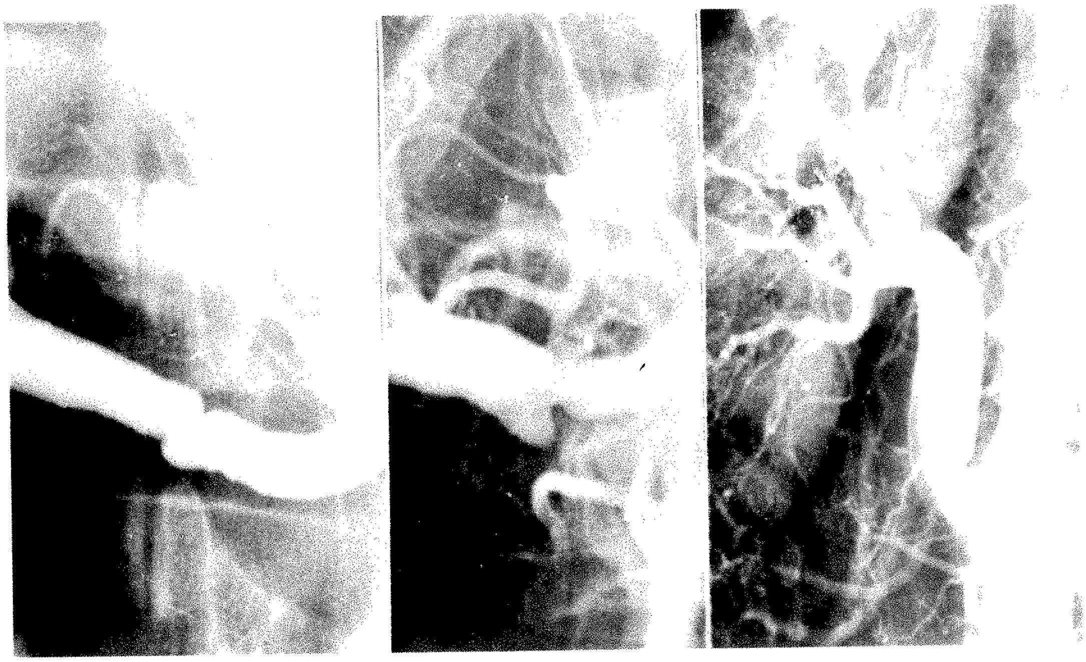

FIG. 1. Arteriograms showing: (Left) Stenotic right renal artery; (Center) Thrombosis of right aortorenal bypass graft with patent but stenotic renal artery; (Right) Patent Dacron aortorenal bypass.

onstrated 4½–24 months later; however, none of these patients had had an early postoperative arteriogram. Therefore it was not possible to determine when the thrombosis occurred. In two patients it was possible to perform a second and successful aortorenal bypass graft using a dacron prosthesis (Fig. 1).

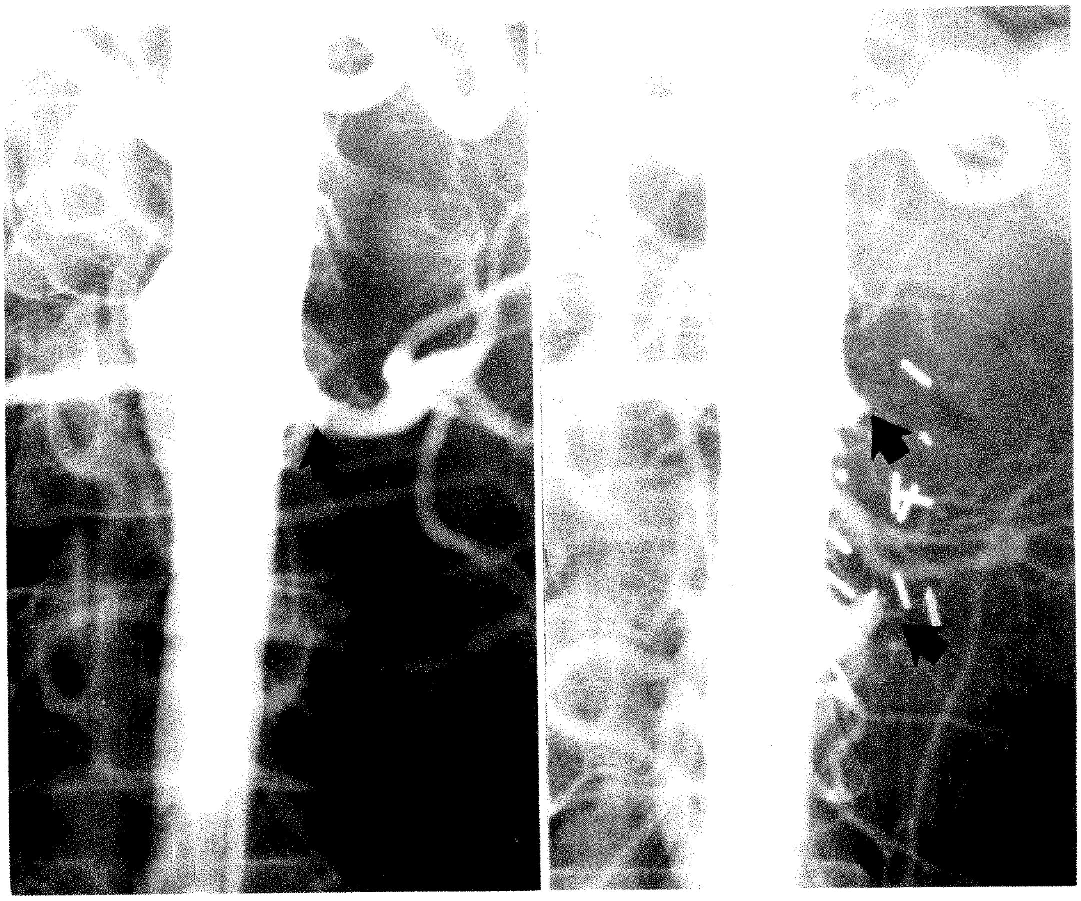

FIG. 2. Arteriograms showing renal artery stenosis and postoperative thrombosis of both the graft and the renal artery.

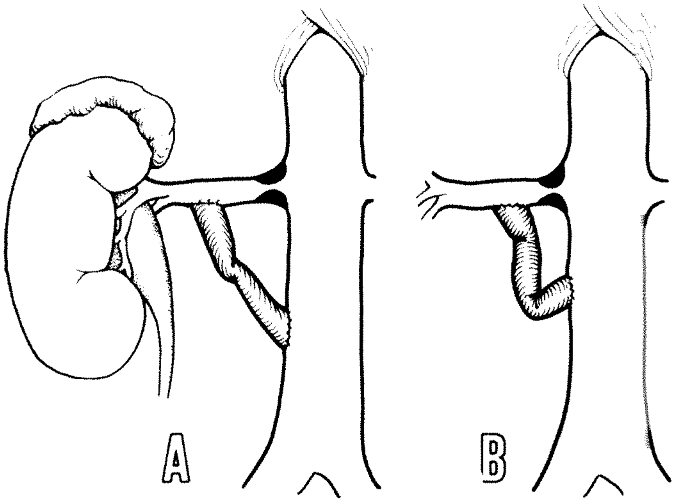

Fig. 3. Drawing depicting: (A) Malalignment of graft producing twisting effect; (B) Kinking from excessive length.

Thrombosis of Vein Graft and Renal Artery

There were seven patients who had thrombosis of both the vein graft and renal artery (Fig. 2). In two patients there was a mild kink in the vein graft as shown in Fig. 3, but there was also a vigorous pulse in the distal graft and renal artery, both grafts thrombosed. Five of the seven patients underwent nephrectomy; in the other two patients nephrectomy was not done because the patient or his physician have opposed another operation. There were two patients who were found to have a thrombosed graft 3–24 months postoperatively, but these patients had not had an early postoperative arteriogram. Any graft that was patent, as determined by arteriography, in the early postoperative period has remained patent on subsequent examination.

Of the 12 vein graft thromboses ten were on the left side and only two on the right. Figure 4 shows the incidence of graft thrombosis each year since 1965. The

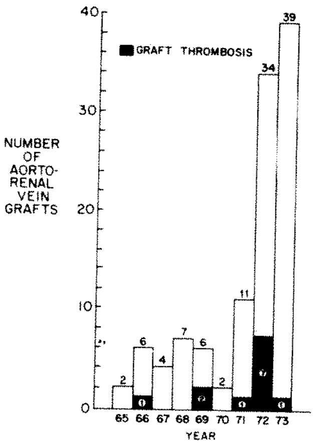

Fig. 4. Graph showing the number of aortorenal vein grafts performed each year with the number of thrombosed grafts also indicated.

operative case load increased sharply in 1972. In 1973 we began using magnification, prolene sutures and modified our operative technique.

The remaining results refer to the 29 patients with 39 vein grafts who have had long term serial followup arteriography one to nine years following operation.

Patent and Normal Graft

Twenty-four of the vein grafts maintained patency and a normal configuration (Fig. 5). These 19 patients ranged in age from 33 to 67 years. Followup ranged from 12 to 108 months. In three patients the early postoperative arteriogram showed a mild to moderate suture line stenosis which resolved and was no longer demonstrable on subsequent arteriograms. Nine patients had fibromuscular dyspasia, the remainder had atherosclerosis.

Dilatation of the Vein Graft

Eight of the 39 vein grafts when studied 2–6 years following implantation were found to be dilated (Fig. 6). The dilatation was uniform throughout the length

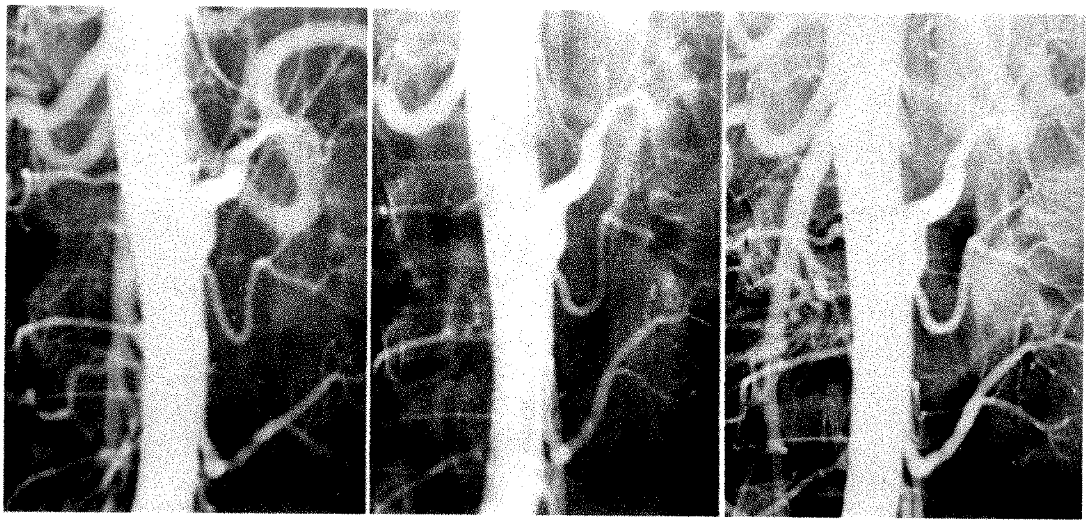

Fig. 5. Serial arteriograms one, four and nine years following saphenous vein aortorenal bypass showing maintenance of original size and configuration.

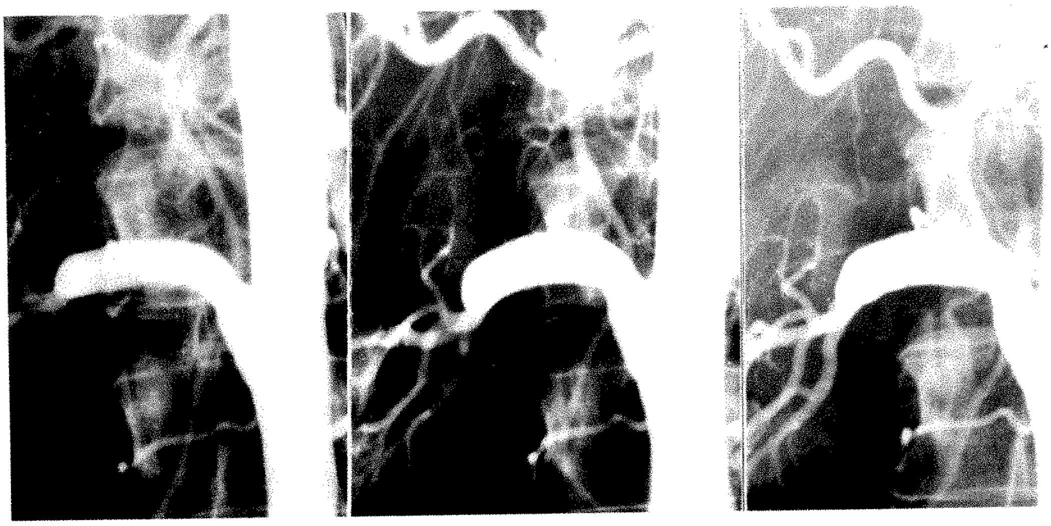

FIG. 6. Serial arteriograms one, two and six years following saphenous vein aortorenal bypass showing mild dilatation of vein graft.

of the vein graft and ranged from a 17% to a 47% increase in graft diameter. None of these grafts has shown a further increase in diameter on subsequent arteriograms. The eight patients ranged in age from 31 to 51 years. Six had fibrodysplastic lesions and the others had atherosclerosis. Each of these patients have maintained a good blood pressure response.

Aneurysm of the Graft

Two vein grafts underwent an increase in diameter of greater than 50% and are classified as aneurysms (Fig. 7). The increase in diameter ranged 87–106%. The development of aneurysmal change was recognized in these grafts three and six years following implantation. In each of the patients there has been no further increase of graft diameter. Each patient has remained normotensive so that nothing more has been done except for periodic repeat arteriograms.

Another patient, a nine-year-old boy who had renovascular hypertension due to left renal artery stenosis and abdominal angina due to celiac artery stenosis and complete occlusion of the superior mesenteric artery, underwent an aortorenal bypass graft and an aorto-superior mesenteric graft three years ago. The hypogastric artery was used for the renal graft and external iliac vein for the superior mesenteric graft. Within three years the hypogastric artery had increased in diameter by 100% and the iliac vein diameter had increased 300% (Fig. 8). He subsequently developed occlusion of his right subclavian and iliac arteries. The iliac artery occlusion necessitated a below the knee amputation. He is now asymptomatic, normotensive and completely rehabilatated with a BK prosthesis and nothing, other than periodic observation, has been done. The etiology of the vascular disease in this patient remains uncertain.

Suture Line Stenosis

Fifteen of the vein grafts showed some degree of suture line stenosis. In ten patients the stenosis was demonstrated in the early postoperative period. The other five patients did not have an early arteriogram and the stenosis was discovered one to two years following

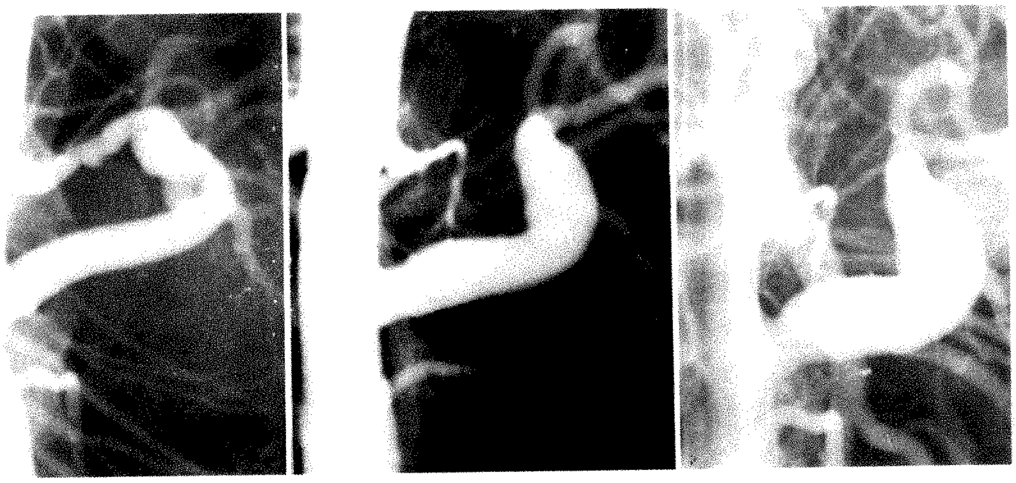

FIG. 7. Followup arteriography one, three and six years after saphenous vein aortorenal bypass demonstrating progressive aneurysmal dilatation.

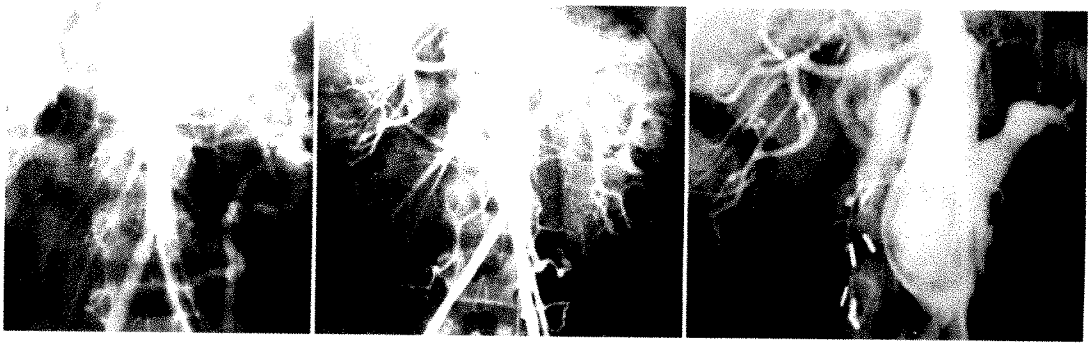

FIG. 8. Preoperative, immediate and three years postoperative arteriograms following hypogastric artery aortorenal bypass and iliac vein aorto-superior mesenteric bypass showing massive aneurysmal dilatation of both.

the operation. In only one patient was the stenosis severe and associated with recurrent hypertension (Fig. 9). In the remaining 14 patients the stenoses have been mild, have remained stable 1–96 months, and they have remained normotensive. Nine of the patients had atherosclerosis and six fibromuscular disease. They ranged in age from 28 to 56 years. In two patients there were stenoses at both suture lines, in five only the aortic suture line was involved and in the other eight patients the stenoses involved the renal artery anastomosis. The recurrent single stenoses involved the left renal artery in six patients and the right in seven. None of the right sided grafts developed a stenosis in its mid-portion as has been noted by the Michigan group and attributed to retrocaval cicatrix formation.[9] As was noted earlier three patients who had stenosis noted on an early postoperative arteriogram were later found to have a normal caliber graft without any narrowing.

Progression of Renal Artery Lesions

In 11 patients the original renal arteriograms showed very mild to moderate and "apparently insignificant" lesions in the contralateral renal artery which have subsequently progressed in severity (Figs. 10, 11). These changes were recognized three months to five years following ipsilateral aortorenal grafting. Seven of these patients had fibrodysplastic lesions and four had atherosclerosis. In three patients the lesion progressed to functional significance and resulted in recurrent RVH which required another aortorenal graft. In the other eight patients the lesions have remained stable, are not functionally significant and RVH has not recurred. These patients ranged in age from 13 to 57 years.

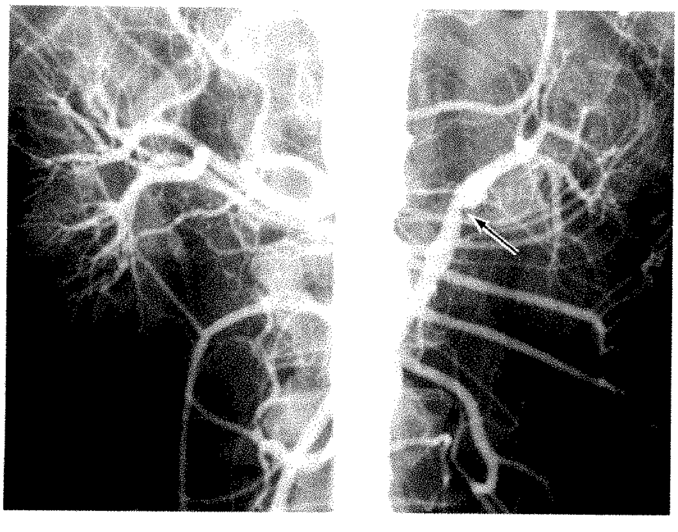

FIG. 9. Postoperative arteriogram of patient with stenotic distal suture line and recurrent renovascular hypertension.

New Renal Artery Lesions

In one patient the initial arteriogram showed the contralateral renal artery to be normal. The followup arteriogram 24 months later showed contralateral renal artery stenosis (Fig. 12). Atherosclerosis was the etiology in that 33-year-old man. RVH recurred and another bypass graft was done. We have not noted development of new lesions in the renal artery beyond an aortorenal bypass graft.

During the followup period three of the 94 patients died. They ranged in age from 33 to 65 years. None of the deaths were related to the vein graft or to hypertension. One death was due to a myocardial infarction, one due to suicide and the final one secondary to an operation for aorto-iliac occlusive disease.

Discussion

There have been a few reported studies of long term followup of autologous saphenous vein grafts used as arterial bypasses or substitutes. Physicians have been understandably reluctant to do followup arteriograms in a patient who is doing well. This is because of apprehension concerning complications attendant to arteriographic studies. This appears to be an unjustified apprehension provided an experienced and skillful arteriographer is available to do the examination. This belief is supported by the data in our report of 754 consecutive abdominal aortograms done in 1973 with but a single serious complication and that one (a femoral artery thrombosis) was easily and promptly corrected.[2] Arteri-

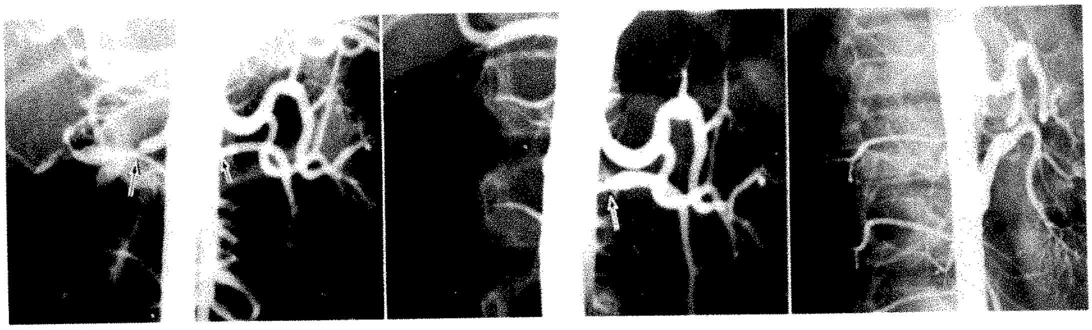

FIG. 10. Serial arteriograms in a child showing right and minimal left lower renal artery lesions (1963). Ten years later severe left lower renal artery stenosis had developed necessitating saphenous vein aortorenal bypass.

ography does carry some risk to the patient but when properly done it is minimal or negligible.

There are several reasons why serial arteriographic followup studies of the various grafts used in renal artery reconstruction are needed. At present saphenous vein, hypogastric artery and dacron prostheses are being implanted as bypasses or replacements of the renal artery in many hospitals throughout the country. The most important consideration is the need to determine which of these arterial replacements, if any, is superior. Each has technical advantages and disadvantages. The fact that many of these grafts are being implanted in relatively young patients adds to the urgency of the problem. There is considerable evidence that autogenous vein grafts in the patient under 20 years of age is particularly susceptible to aneurysmal dilatation. Four of the six vein graft aneurysms occurring in aortorenal grafts reported by Stanley, *et al.* were in patients under 20 years of age.[9] These four aneurysms occurred in a group of 12 children subjected to renal artery reconstruction with a saphenous vein.

The Michigan group has previously reported a study similar to the one herein recorded.[9] Table 3 compares the two studies. The incidence of vein graft thrombosis in the two groups is similar as is the incidence of aneurysm formation, thereafter the results become divergent and for the most part unexplainable. There is a difference in the operative technique employed in the two groups of patients. The vast majority of the cases in the Michigan group had an end to end anastomosis between the saphenous vein and the renal artery; whereas an end to side anastomosis was done in most of our patients. Whether this difference influenced the results is unknown. It should be strongly emphasized that in Tables 2 and 3 the stenoses for the most part (14 of 15) were mild, insignificant and that patients have maintained a good blood pressure response. The same is true for the blood pressure in the patients with dilatations and aneurysmal changes. Finally, two of the patients with graft thrombosis had a second and successful arterial reconstruction while three others have not yet accepted that option.

In our experience, thrombosis of the vein graft, when it occurs, does so in the early postoperative period and is probably related to technical, operative errors. Others have reported a similar belief.[9] The evidence supporting this belief is that every graft which was shown to be patent 7–10 days following the operation has remained patent on subsequent arteriography. Obviously, many

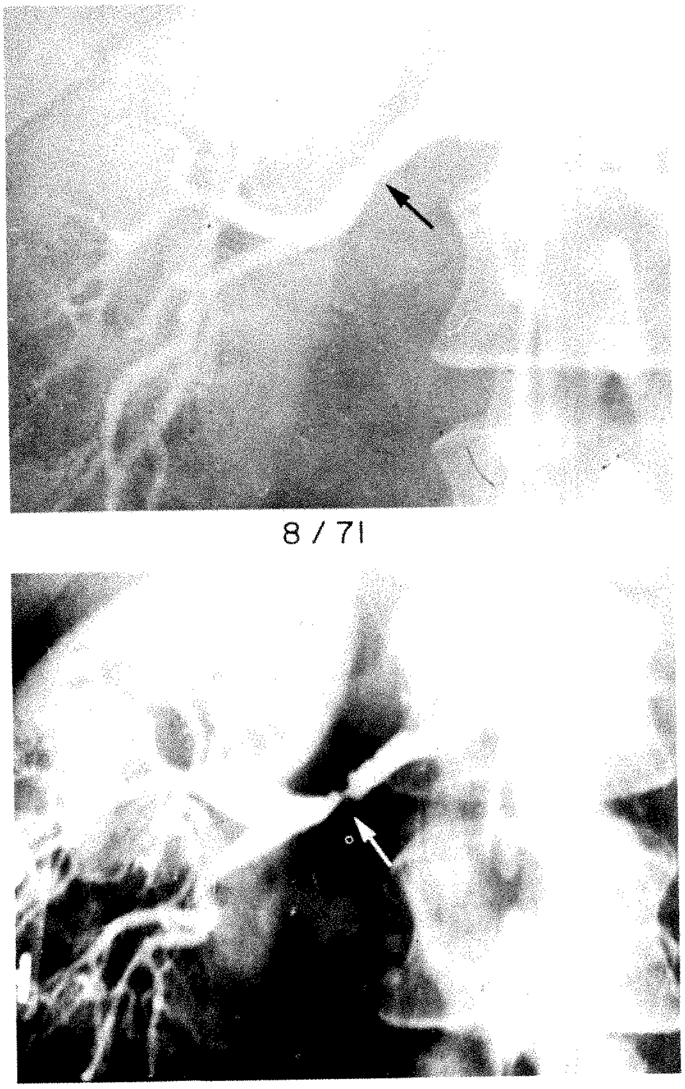

FIG. 11. Selective right renal arteriograms showing dramatic progression of the renal artery stenosis which occurred in a three month period.

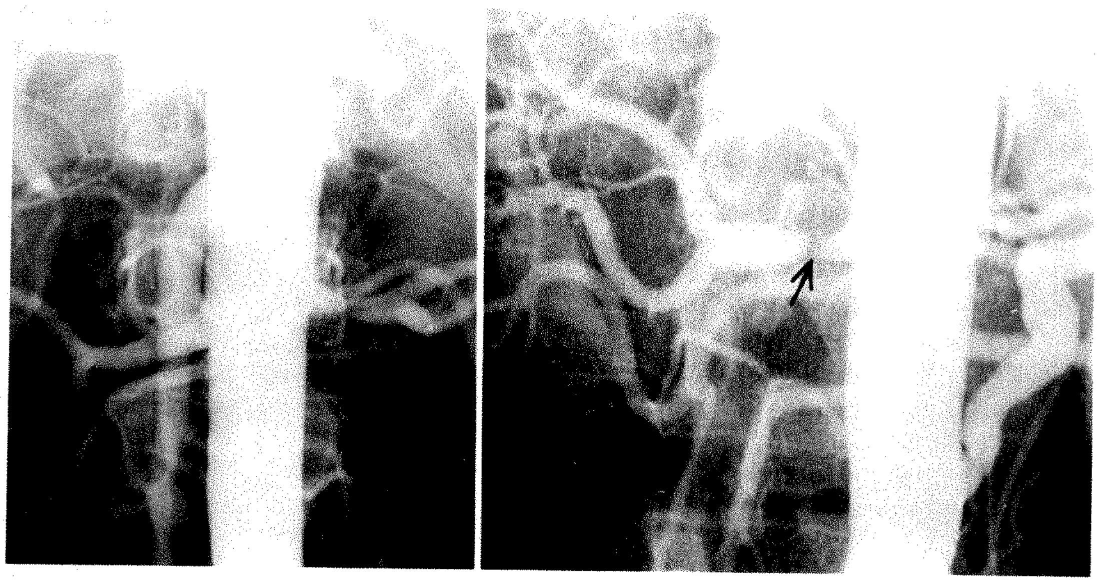

FIG. 12. (Left) Arteriogram prior to left renal artery bypass showing normal right renal artery. (Right) Two years later hypertension recurred and arteriogram showed a patent left renal artery bypass and a severe, new right renal artery stenosis which was successfully bypassed.

factors can contribute to graft thrombosis. Kinking or longitudinal twisting of the graft, as shown in Fig. 2, are two notable ones. When doing the anastomosis between the graft and the lateral wall of the aorta, if one rotates the aorta to the contralateral side in order to facilitate the procedure, it is easy to make the length of vein graft too great. When the aorta is de-rotated the vein graft is redundant and may kink.

One unique virtue of doing an end to side anastomosis between the graft and the renal artery is that if the graft thromboses, the renal artery may not. On six occasions (one from elsewhere and not included in this report) we have seen graft thrombosis but continued, although stenotic, patency of the renal artery. In three instances we have done a successful second bypass graft. As a rule when an end to end vein graft thromboses, so does the renal artery.

The uniform dilatation of saphenous vein grafts implanted in the renal artery is poorly understood. By contrast, saphenous veins implanted in the femoropopliteal system or in the coronary arteries have frequently undergone fibrotic stenosing changes.[1,5,7,10] In Szilagyi's report, an arteriographic followup of 260 saphenous veins implanted into the femoropopliteal artery, ten of the vein grafts developed aneurysmal dilatations while 75 developed stenosing lesions.[10] Furthermore, the aneurysmal dilatation did not involve the entire length of the femoropopliteal vein graft, as is the case with the renal artery vein grafts, but rather were localized dilatations of a short segment of the vein graft. Renal blood flow is much greater than coronary or femoral artery flow. Flow meter studies on coronary vein bypasses average 70–90 ml/min, whereas renal bypass blood flows average 300–400 ml/min. The dilatation of the vein graft in the renal artery usually develops slowly over a period of several years, usually reaches a given degree of dilatation and remains stable thereafter. In most patients if the initial blood pressure was favorable, it has remained so in spite of the dilatation.

TABLE 3. *Comparative Results of Saphenous Vein, Aortorenal Grafting*

Vein Graft Configuration	Vanderbilt Number of Grafts*		Michigan Number of Grafts*	
Thrombosis	12/89	13%	9/100	9%
Normal	24/39	62%	29/74	40%
Dilatation	8/39	20%	33/74	44%
Aneurysm	2/39	5%	6/74	8%
Stenosis	15/89	17%	7/74	9%

* The incidence of thrombosis and stenosis are based on early and/or late arteriographic studies. The incidence of the other changes is based on arteriograms done 12–108 months following operation.

Currently there is much interest in whether the method of harvesting, handling and preparing the saphenous vein for implantation influences subsequent graft performance and configuration. Evidence has been presented which indicates that forceful dilatation, distension or excessive adventitial disection of the graft has a deleterious effect.[9,10] Placing the vein in saline, especially at room temperature, has also been indicted as a cause of injury to the vein. Storage in cold Ringers lactate solution, cold blood, cold glucose and other solutions have been recommended. It is far too early to evaluate the evidence supporting these concepts. Certainly, more investigation in this area is urgently needed.

When the severity of the dilatation of the vein graft caliber exceeds 50% of the original diameter it has been classified as an aneurysm. We have had two such cases, both have remained normotensive and nothing further has been done except for periodic reevaluation. Of the six cases of aneurysmal vein grafts reported by the

Michigan group, two reached proportions which prompted resection of the vein graft and creation of a second aortorenal vein graft. Both of the original vein grafts revealed degenerative changes of a rather nonspecific nature. These aneurysmal changes in the saphenous vein implanted in the renal artery are cause for great concern. However most of the aortorenal vein grafts have held up quite well. It is likely that they should *not* be used in children. The saphenous vein in the child is structurally an anatomically different than in the adult.[9] The arterial blood supply of the saphenous vein in the child and in the adult are apparently different. The frequency of aneusysmal dilatation of vein grafts in children has been attributed to these differences. Information concerning the long term performance of the hypogastric artery implanted in the renal system is not yet available. Early in our experience we felt that the dacron prosthesis, implanted in the renal artery was more likely to thrombose. What we were actually comparing was our first three or four year experience with our second three to four year experience with renal arterial revascularization. In actual fact, in our experience, if the Dacron graft was initially patent, it has remained patent on subsequent examinations. If the renal artery beyond the stenosis is large (6–8 mm in diameter) and the saphenous vein is less than 4 mm in diameter, we do not hesitate to use a Dacron prosthesis, especially in a child. The ultimate fate of these grafts remains to be determined. We have never seen or heard of a false aneurysm developing in an anastomosis between the saphenous vein and an artery. False aneurysm formation in a Dacron prosthesis-renal artery anastomosis has been observed.[8]

We have rarely encountered a functionally significant stenosis in an aorto renal vein graft (e.g. a stenosis causing recurrent RVH). Stanley *et al.* reported a 9% incidence of such stenoses.[9] The etiology of these stenoses is also obscure. Once again vein graft handling has been incriminated as has the retrocaval course of a right aortorenal graft. In the latter type of stenosis retrocaval hematoma and subsequent cicatrix formation has been cited as the inciting factor in causing a stenosis in the mid-portion of a right aortorenal vein graft. We have not observed a stenosis other than at the suture lines in any of our patients. Conkle, et al have reported experimental canine studies which indicate that both arteries and veins when transplanted in an arterial system develop proliferative intimal lesions which might produce significant stenoses—these studies were done in the femoral arteries of the dog.[3] The one vein graft that we have recovered following thrombosis showed similar fibrotic intimal proliferation.

Another observation encountered in this study was the frequency of development of new or progressive stenotic lesions in the contralateral renal artery. The importance of this observation relates to avoiding nephrectomy in patients with RVH. In many of the early reports on treating patients with RVH, nephrectomy was the mode of treatment in over 50% of the patients. It is now apparent that nephrectomy should not be done except in the case of a destroyed kidney or in patients who are uncontrollable and whose renal artery can not be reconstructed.

The most satisfying observation in the study was the sharp decline in graft thrombosis in 1973 as compared to 1972. This improvement is attributed to modifications in operative technique.

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DISCUSSION

DR. GEORGE COOPER MORRIS, JR. (Houston): Our experience in the long-term state of the vein in the renal artery position has been exactly similar to Dr. Foster's and his group. True aneurysms developing in adults have been extremely rare in our experience.

(Slide) Here is an example of a patient who has been followed through the years, who had a preoperative study in 1962, and then the immediate postoperative study. It has the appearance of a vein, without uniform conformity, but most of these veins arterialize, as it were, to a certain extent and get a more uniform appearance, which you can see in 1969.

This same patient returned last year with iliac occlusive disease, and again his vein graft in the left renal artery appears normal.

However, in children the story is a little different. Renal artery problems in children are infrequent, and yet I have had three aneurysms develop after saphenous vein autograft repairs. This is an example of one, a young boy of eight who had a high grade stenosis distally in his right renal artery which might have been of traumatic origin.

An early followup study shows a normal appearance after patch angioplasty bridging over the branching complex on the right, much as Dr. Foster has done. The boy remained normotensive, but I did get him back for a followup study, having had this experience previously in two other children, and again I saw this development of an aneurysm after six years.

I do not know whether the saphenous vein is infantile, or lacks elastic tissue, or whatever, but it does not seem to work well in children. The hypogastric artery in the child is a better substitute.

The hypogastric artery is not a good graft in the adult because it is usually the first artery to develop atherosclerosis. Here is an example of a congenital occlusion of the right renal artery in a child, and you can see the early and late phases in the arteriogram with total occlusion, but a good kidney.

(Slide) After operation, you see the missing right hypogastric artery and its appearance as a right renal artery. It is probably important to use interrupted sutures in children.

Dr. William J. Fry (Ann Arbor, Michigan): A year ago we presented our results with 100 consecutive vein grafts; and as pointed out by Dr. Foster, we were concerned principally with aneurysmal change, stenosis, and thrombosis. I think expansion is probably not something to be worried about, as these patients have continued to do well. Their grafts have not enlarged after their immediate expansion, and continue to function extremely well. With the technique of a widely spatulated end-to-end anastomosis we have seen no stenosis at the suture line.

Of our six graft aneurysms, four occurred in children. Only one of those four had to be replaced, and the others have leveled off, have not dilated any more beyond a two-year period and continue to function well. Obviously, we are worried about them.

One of the aneurysms we replaced in the adult group was a poststenotic dilatation, and I would like to emphasize that we believe the stenoses that occurred were secondary to rough handling of the vein at the time of operation, where a large occluding clamp was placed on the vein graft prior to the distal anastomosis. This provoked us to stop using crushing clamps. If the vein graft must be clamped during the course of the procedure, we should prefer to use microvascular clamps that will not injure the graft.

We agree with Dr. Foster that thrombosis is a factor of technical failure. One has a high-flow system, and there is no reason for immediate thrombosis of the graft. Thrombosis is secondary to lack of systematic anticoagulation, poor technique or improper selection of patients.

We have continued to use vein grafts in our children. We now have a group of 32. They have done well, and we have had no further aneurysms since we have procured our vein grafts with more care. I do believe, however, that veins are not perfect. These grafts must last a long period of time, and it is important to continue to watch them closely.

(Slide) This is a vein graft that was preserved in normal saline at room temperature for 15 minutes, and you can already see the amount of separation of the intima from the vein graft wall.

(Slide) This represents a vein graft preserved in room temperature Hartmann's solution for 15 minutes. Notice the discoloration and puffy appearance of the vein graft.

(Slide) This is a vein graft preserved and cooled in heparinized blood for one hour. You can see the integrity of the vein graft has been maintained with a relatively normal appearance. Certainly, preservation of the vein graft at the time of operation is an important consideration and one that we had not paid attention to until we did our survey. This is particularly important in young people. The majority of our patients are young ladies with fibrodysplastic disease. They have many years ahead of them, and these grafts must serve them over a long period of time.

Professor Lars-Erik Gelin (Goteborg, Sweden): The patency in Dr. Foster's series of patients was impressive. Two of 28 cases with fibromuscular stenosis occluded, however, which stresses the risk of failure at reconstruction of this otherwise benign lesion.

Patency will depend on the efficiency and smoothness in detailed reconstruction of small arterial branches.

I advocate an extracorporeal approach for repair of such distal renal artery stenosis. It will allow a very detailed and proper reconstruction at the workbench in a totally bloodless state, as a safer procedure than in situ repair.

(Slide) Let me illustrate this with a case of distal renal artery stenosis in a 40-year-old woman with a single kidney. She had a progressive hypertension with a blood pressure of 240/120 with maximal doses of antihypertensive drugs, permanent headache, serum creatinine 1.2; inulin clearance was 66 ml per minute.

(Slide) At excision you can see the branching off, and two stenotic areas. After resection of this region, reconstruction was done using saphenous veins, and reimplantation. The followup angiogram shows a good perfusion, excellent renographic phase.

After reconstruction, her serum creatinine decreased to 0.6. Inulin clearance increased to 80 ml per minute, blood pressure was 130/80, without any drugs.

Our experience from 23 extracorporeal kidney reconstructions has convinced us that the procedure is safe and permits ideal conditions for detailed surgical repair without the pressure of time. I believe that the ischemia time with *in situ* repair contributes to an increased renal vascular resistance, and thereby decreases flow through the reconstructed region and thrombotic occlusions. Failure of arterial reconstructions to correct hypertension may be due to arterial occlusion to ischemia injury to the renal parenchyma and to extrarenal causes. The first two might be more readily controlled with the extracorporeal method.

Dr. Richard H. Dean (Closing discussion): As Dr. Foster has stated, we have also had concern regarding long term results in regard to dilatation and aneurysmal formation of the vein graft, and also feel that this is much more common in children (slide).

This child, for example, had a severe, bizzare form of juvenile fibromuscular dysplastic disease. He has multiple arteries involved, including his left renal artery and his superior mesenteric artery.

Immediate postoperative arteriograms following an iliac vein anastomosis to the superior mesenteric artery and a hypogastric artery to the left renal artery showed patent grafts.

Within three years following this, both of these had undergone severe dilatation; approximately 300% in the iliac vein, and 100% dilatation in the hypogastric artery.

Although we do know that it occurs from saphenous veins, the dilatory phenomenon late in followup in these patients is not limited to veins, but can also be seen in arterial reconstructions.

Another point brought out by all the discussants that we feel is extremely important is that of technique. Obviously, if the vein thromboses a week following operation, the opportunity for even dilatation or aneurysmal formation is lost, and the importance of operative technique cannot be minimized.

In regard to Dr. Gelin's comments concerning extracorporeal circulation, we have now done this in six patients also. In the first patients we used a modification of the Belzer pump, leaving the ureter intact. To date all six of these patients' grafts have remained open and have not shown any dilation or thrombosis.

Finally, in the childhood age group we have not used the hypogastric artery, but have usually preferred to use Dacron grafts. Although in our earlier experience with Dacron grafts we felt there was an increased thrombosis rate, we now feel this probably simply reflected our early experience, and in our later followup of these patients in which the Dacron graft was used, the patency rate has been very similar to that of saphenous vein grafts. Dacron works quite well in children in which there is aneurysmal dilatation distal to the stenosis, at which point the Dacron graft can be easily anastomosed.

Surgical Treatment of Gastroesophageal Reflux in Infants

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Thirty-one infants less than a year of age underwent surgery for correction of pernicious gastroesophageal reflux. Severe growth retardation from persistent vomiting was the single most important indication for surgery (25 patients). Recurrent aspiration penumonitis was another serious sequella of reflux and necessitated surgery in six patients. The diagnosis of gastroesophageal reflux was confirmed by barium swallow in all children, and in 17 a concomitant hiatal hernia was demonstrated. Patients selected for surgery were first treated conservatively unless they showed significant esophagitis or had a major portion of stomach in the chest. Babies treated early in the series had Allison repairs (7 transabdominal, 2 thoracic). Twenty-two subsequent patients have had Nissen fundoplication, and two gastropexies were performed. In 15 patients, significant gastric outlet obstruction required a complementary pyloroplasty. Four infants required a second surgical procedure because of recurrence. Two of the four patients had Nissen procedures with good results, one following a Boerema gastropexy and one following an Allison repair. The other two patients needed revision after fundoplication. There was no mortality. Twenty-eight children have been followed 6 months–8½ years. All have excellent nutritional status and are following normal growth curves. Study of these patients indicates the need for early diagnosis and medical or surgical therapy for all infants with major gastroesophageal reflux.

GASTROESOPHAGEAL REFLUX with or without hiatal hernia is a major cause of recurrent vomiting and failure to thrive in newborns and young infants. Although the symptom complex of gastroesophageal reflux in babies has become better recognized, the criteria for surgical intervention in these young patients have not been well defined. Older children and adolescents with hiatal hernia and reflux have symptoms indistinguishable from those seen in adult patients. In these older children, the indications for surgery are substernal distress, uncontrolled pain, evidence of inflammatory changes in the esophageal mucosa, bleeding or frank stricture; they will not be considered further here. The purpose of this report is to present the clinical data on 31 infants under a year of age who have had surgical correction of gastroesophageal reflux. They have been followed from six months to eight years. The term hiatal hernia has been discarded in these patients so that attention may be focused on the effects of pernicious gastroesophageal reflux in infants.

Clinical Material

Thirty one patients less than one year of age have had surgical correction of gastroesophageal reflux at the Children's Hospital of Washington, D. C. The patients were treated between January 1964 and July 1973. There were 22 boys and nine girls. The duration of symptoms was from three days to 11 months and all patients had been symptomatic from the early weeks of life.

In this clinical study the major two symptoms of gastroesophageal reflux were persistent vomiting and failure to thrive (Table 1). Infants with this condition usually had some form of regurgitation or frank vomiting from birth (97%); on many occasions the vomiting was projectile in character and initially suggested a diagnosis of pyloric stenosis.

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Sponsored by H. William Clatworthy, Jr., M.D.

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TABLE 1. *Major Symptoms of 31 Patients with Gastroesophageal Reflux*

Vomiting	30	97%
Failure to Thrive	25	81%
Pneumonia	6	19%
Bleeding	2	6%

Weight loss or delayed weight gain with retardation of developmental landmarks was the second most common presenting symptom and was found in 81% of the patients. These babies were below the tenth percentile on their growth charts or showed a marked falling off of growth progression. Six patients less than two months of age were so severely malnourished that they were admitted to the hospital because of marked inanition. Compared with normal siblings, one-third of the patients were markedly retarded in developmental landmarks such as sitting, standing, walking and dentition.

Recurrent aspiration pneumonitis was seen as the presenting complaint in six patients (19%) and anemia secondary to blood loss from esophagitis was encountered in two patients (6%). A number of infants presented with persistent vomiting but without impairment of their growth; in two such patients, the inability of the mother to cope with the infant's constant vomiting caused serious disruption of the family, and surgery was undertaken.

Diagnosis

The diagnosis of gastroesophageal reflux was confirmed in all patients by barium swallow. In 17 examinations (some patients had more than one), projection of gastric mucosal folds was seen above the diaphragm with the gastroesophageal junction in the chest (Fig. 1). Free gastroesophageal reflux without hiatal hernia was found in 16 patients (Fig. 2). In 15 patients delayed gastric emptying was noted on the preoperative roentgen studies. In 17 babies esophagitis was suspected by x-ray; esophagoscopy was performed in this latter group. Ten showed evidence of mild to severe esophagitis, and in all cases so studied, free reflux of gastric content though the gastroesophageal junction into the esophagus was observed.

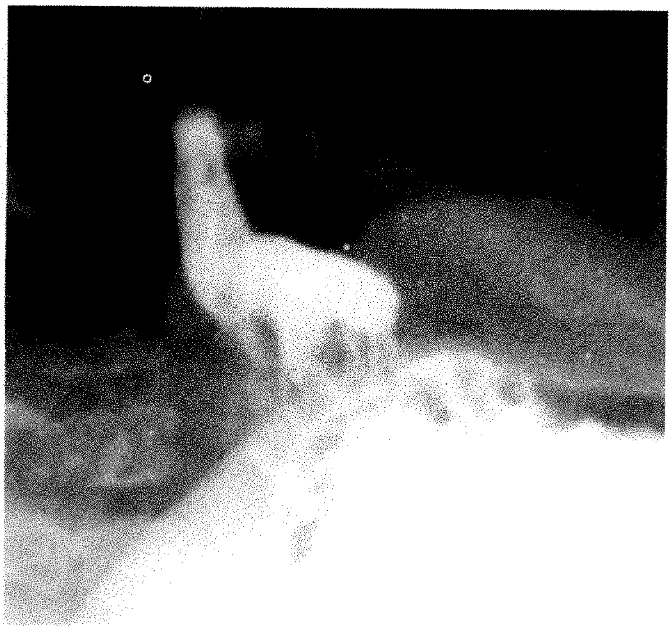

FIG. 1. Barium study in 4-month-old infant showing small hiatal hernia. There is no evidence of esophagitis. Gastroesophageal reflux was prominent.

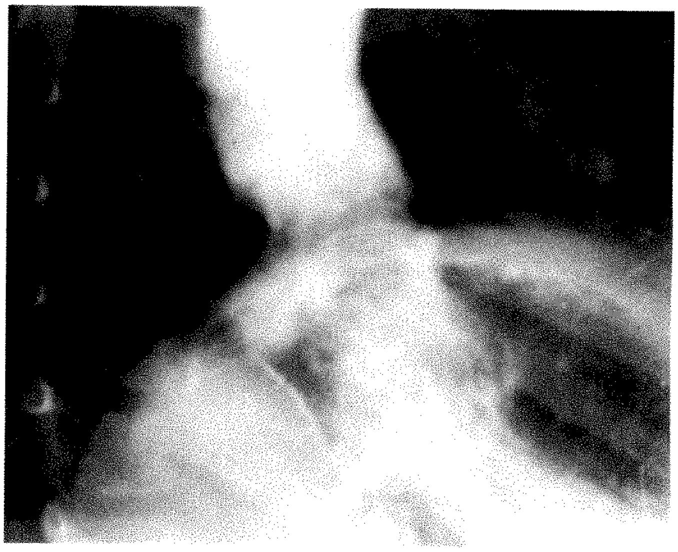

FIG. 2. X-ray taken after completion of barium swallow showing gastroesophageal reflux. No gastric herniation is seen.

Gastric analysis was performed in 11 infants with demonstrated gastroesophageal reflux and compared with other disease entities in neonates and with normal infant controls. The method of analysis was developed in our clinical unit specifically for use in infants, using a principle of gastric wash. Volume, pH, chloride, total acid and the rate of acid formation were determined and evaluated with respect to the weight of the patients. While significant and highly significant deviations from controls were found in certain infantile conditions such as pneumonia (more alkaline) and the short gut syndrome (more acid), the studies of babies with gastroesophageal reflux showed no difference from control data (Table 2). Satisfactory esophageal pressure study techniques for infants have not been possible in our hands, and so this type of investigation has not been done in these patients.

Most infants were treated medically for at least three months before being considered as failures of conservative treatment. The medical regimen consisted of thickening all formula feedings, usually with rice cereal, and propping the infant upright 24 hours a day.[11] Five

TABLE 2. *Comparative Studies of Gastric Secretion in Infants*

Catagory	Number	Gastric pH	Total Acid*	Acid Rate†	Weight-adjusted‡ Rate	Chloride	Pepsin	Urine pH
Well (controls)	38	3.2	6.2	.15	54	133	440	6.3
Hiatal hernia	11	3.6	6.2	.15	45	144	424	7.6
Short gut	7	2.4	19.1‖	.58‖	151‖	161	550	5.5
Bronchiolitis	22	4.8‖	4.6	.11	28‖	134	231§	6.0

* mEq/100 ml gastric juice.
† mEq/100 ml gastric juice/min.
‡ Rate of acid formation = (mEq/100 ml gastric juice/min/kg body weight × 10^3)
§ Significant $p = 0.05$.
‖ Highly significant $p = 0.01$.
From Avery, Randolph and Weaver[2]

of the six infants who were seen with severe nutritional depletion secondary to reflux were treated medically in the hospital for only two weeks. Because their gains were minimal in spite of intensive nursing care and strict adherence to the medical program, operation was carried out at the end of only two weeks medical trial in each of these patients (Fig. 3).

The criteria used for operation in these 31 infants were: 1) persistent vomiting of all or most of each feeding after sustained, rigorous medical regimen plus one of the following; 2) absent or markedly depressed weight gain; 3) severe malnutrition and no response to two weeks of intensive medical treatment in the hospital; 4) recurrent pneumonia; 5) gastrointestinal bleeding from esophagitis; 6) major displacement of the stomach into the chest; or 7) serious family disruption by the incessant vomiting.

During the period of this clinical study, two major operative techniques were used. From 1964 to 1967, nine patients were operated on using the modified Allison[1] technique, seven via the abdominal route, one using the standard transthoracic Allison repair and one with a thoraco-abdominal approach. From 1968 to the close of the study, 22 patients were repaired by the fundoplication technique of Nissen,[21,22] including two reoperations. Two gastropexies were performed. Since gastric outlet obstruction was discovered in 15 patients, on upper gastrointestinal x-ray study, pyloroplasty was done as a complementary procedure on these patients. For these small subjects, a special pyloroplasty has been used which employs a pedicle of the gastric antrum advanced into the proximal duodenum.[23] The procedure has the dual advantage of minimal operative dissection and maximal channel size; both of these features are important in the infant.

Early Results of Operation

Twenty eight patients had prompt relief of symptoms. Vomiting ceased abruptly and patients began to gain weight dramatically (Fig. 4). In most cases, the infants had accelerated weight gain and reached normal weight levels for their age within six months. The medical regimen was discarded and normal feeding was instituted and tolerated well by all of the babies in the early postoperative period. Of the two infants who underwent Boerema gastropexy, one did well and required no further surgery. The second was an immediate, total failure with continued vomiting and weight loss; one month later a Nissen fundoplication was performed. This infant showed excellent progress after the second operation.

There were no operative deaths. One child died 15 months after repair, of unrelated causes. Two infants, one of whom had presented with recurrent aspiration, had pneumonia in the postoperative period. Staphylococcal sepsis occurred in one patient and was successfully treated. Duodenal perforation occurred from a feeding catheter placed in a four week old infant to support critical nutritional deprivation. The infant recovered after surgical closure of the perforation.

In one infant, delayed gastric emptying was noted in the postoperative period and pyloroplasty was undertaken as a separate procedure.

Recurrence

There have been four recurrences. One patient had a Boerema gastropexy with no relief of symptoms; a Nissen fundoplication was performed with good results. One baby who was repaired by the Allison technique was asymptomatic for nine months and then had recurrence of vomiting. UGI series showed an anatomic recurrence of hiatal hernia with gastroesophageal reflux. A second operation employing fundoplication was carried out, and he promptly became asymptomatic with an excellent result at 7 1/2 year followup. Poor feeding in a patient who had a Nissen fundoplication 2 1/2 years previously led to examination by UGI series, which demonstrated recurrent gastroesophageal reflux. His parents have declined further surgery. The fourth patient with recurrence continued to vomit after surgery. GI series showed anatomic recurrence and delayed gastric emptying. A pyloroplasty was performed, but vomiting

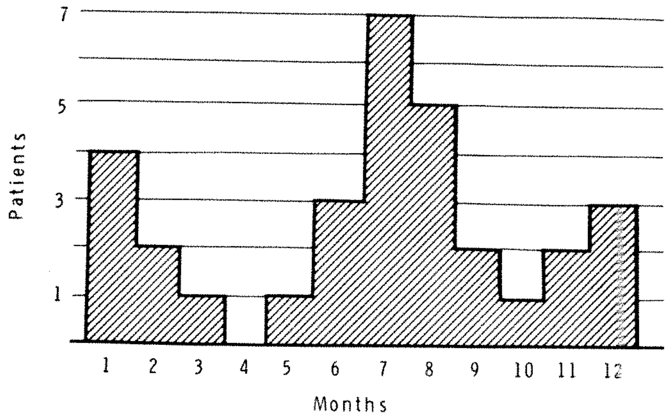

FIG. 3. Graph depicts the age at surgery of the 31 infants. Seven patients required surgery before three months of life.

persisted. Repeat herniorrhaphy and concomitant vagotomy were subsequently performed elsewhere; nutritional improvement was slow but steady, and the child is now well two years after the last operation.

Long-Term Followup

Three patients were lost to followup, leaving 28 children who have been followed from six months to 8½ years since correction of the gastroesophageal reflux. Of this group, 25 patients have excellent final results. These include two patients with recurrent reflux who have been brought to satisfactory status by a second operation. All 25 children are now growing normally and their weight gain has been changed dramatically from the preoperative state and is now within percentile curves appropriate for their heights and body habitus (Fig. 5). Those who have reached school age are producing results comparable to their peers. The three remaining patients are in satisfactory status but are not classified as good results. One child has deformities caused by maternal ingestion of Thalidomide during pregnancy and has a major disturbance of carbohydrate metabolism. Although surgical correction of reflux was prompt and complete, this patient has remained below the third percentile in weight for age. The other child is normally developed by physical and psychological parameters but is very small for his age, measuring below the third percentile; no reason for this is apparent. The third patient was lost to followup two years postoperatively, but during those two years required dilatations every few months for excessive narrowing at the gastroesophageal junction; in spite of this problem, the child's growth and development had been markedly improved by surgery.

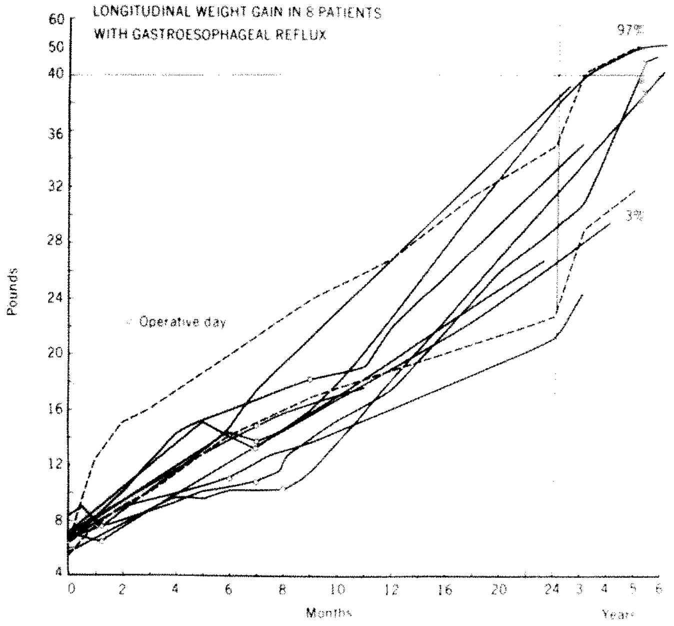

FIG. 4. Linear growth studies in eight patients diagnosed as failing to thrive because of gastroesophageal reflux. Prompt response to surgery is demonstrated in all but one of the infants.

Of nine patients undergoing the Allison procedure, one had a recurrence and one had esophageal narrowing at the site of repair which responded to a single dilatation. Of 20 primary Nissen procedures there were two recurrences; two infants showed narrowing at the site of repair which responded to one and two dilatations respectively.

Discussion

Hiatal hernia and gastroesophageal reflux is found in all age groups from infancy to the aged. The uniquely deleterious effects of this condition in infants have been recognized with increasing frequency in the past few years.[10,14–16] The spectrum of symptoms from gastroesophageal reflux is distinctly different in infants than in the adult. Substernal distress, eructation and dysphagia are well known manifestations of hiatal hernia in the adult. In infants the predominant symptoms of gastroesophageal reflux are vomiting, significant growth retardation and aspiration pneumonia.

In the babies it is not always possible nor even particularly important to demonstrate gastric herniation at the esophageal hiatus. Our clinical observations have led us to the conclusion that the radiologic or endoscopic visualization of an anatomic gastric herniation at the hiatus is not a prerequisite for the diagnosis of pathological gastroesophageal reflux in infants. The signal abnormality is the absence of the normal valvular mechanism at the gastroesophageal junction, which allows unimpeded reflux of gastric content.

In 1947 Berenberg and Neuhauser[3,20] introduced the term chalasia for babies with abnormal relaxation of the esophagogastric sphincteric mechanism. They showed, and pediatricians everywhere have subsequently con-

TABLE 3. *Operative Results in 31 Infants with Gastroesophageal Reflux*

		Results			
Type of Operation	Number of cases	Good	Recurrence	Satisfactory after Reoperation	Lost to Followup
Reconstruction (Allison)	9	6	1	1*	2
Fundoplication (Nissen)	20	17	2	1	1
Gastropexy (Boerema)	2	1	1	1*	
Totals	31	24	4	3	3

* Nissen fundoplication.

firmed, that a majority of infants with chalasia can be treated successfully by propping them in an upright position.[11] In the pediatric world, for patients under a year of age, the term chalasia and gastroesophageal reflux are used interchangeably. Remarkably, the reflux which is demonstrable on barium swallow x-ray studies in such infants spontaneously disappears by 15–18 months of age, the age when the baby assumes the upright position by standing and walking.

Because this phenomenon of gastroesophageal reflux seems to have a spontaneous resolution by the time the baby reaches 15 months of age, the condition has mistakenly been regarded as normal in the infant. It is true that there may ultimately be resolution of the problem by a yet undefined maturation of muscular relationships at the hiatus. However, this fact should not detract from the debilitating nutritional disturbances occurring in a very specific subgroup of these infants during their first and most unique year of development.[12] This deprivation may have a lifetime of consequences.

Attention should be focused on those babies whose gastroesophageal reflux is not responsive to the medical routine. In an earlier report,[17] 10 of 35, or 28% of the infants we studied were considered failures of conservative therapy. As experience has increased and our criteria for surgery have sharpened, approximately 15% of all babies studied or seen in consultation have been considered as medical failures. Not only is the vomiting persistent and troublesome, but the consequences of seriously restricted nutrition are clinically manifest in these infants, whose body growth and temporal landmarks are measurably delayed to a significant degree at a crucial time in their development. It has been well shown in the laboratory that nutritional deprivation has a deleterious effect on the developing brain.[12] While not yet a measured phenomenon in patients with this disorder, the ominous cause-and-effect inference is inescapable.

All infants below the age of two months who require hospitalization because of malnutrition secondary to gastroesophageal reflux and who do not respond promptly to conservative therapy should be operated on. In five such infants in this study, the trial of thickened feedings and propping was limited to two weeks. In these very young patients, the nutritional state may be precarious. While babies with major inanition might now best be prepared for surgery by a course of intravenous hyperalimentation, the dramatic weight gain seen immediately after surgery in this small group of five newborns is noteworthy. For 13 of the babies operated upon in the earlier years of this clinical study, weights were not regularly recorded in the months subsequent to the immediate

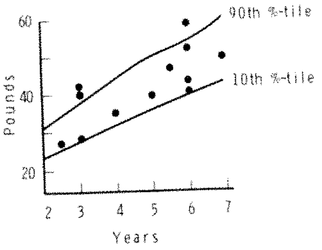

FIG. 5. Postoperative weights in 12 infants with gastroesophageal reflux followed longer than two years showing all are within the weight norm for age.

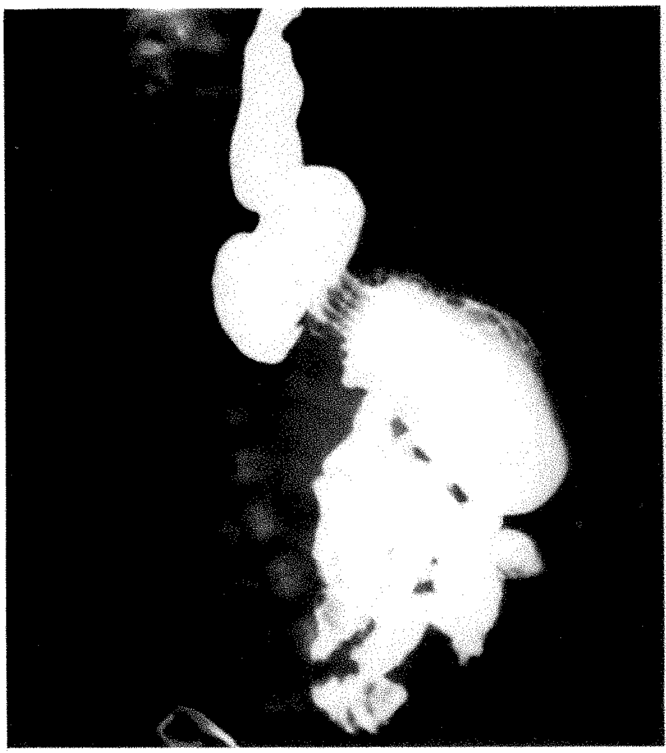

FIG. 6. Barium study on 3-day-old infant admitted to the hospital because of vomiting. With major displacement of stomach into the chest as in this patient, prompt surgery is indicated.

postoperative period. However, long term followup has confirmed the immediate postoperative impression and later weight gain has continued along normal curves (Fig. 5).

Another separate indication for surgery is found in the large congenital hernia with major displacement of the stomach into the chest. A three-day-old infant was operated on without any trial of medical therapy when he presented with vomiting of all feedings, dehydration, and a huge hiatal hernia on upper gastrointestinal series (Fig. 6). Such a large hernia constitutes a contraindication to conservative therapy. Older infants between the ages of three months and twelve months who persistently demonstrate poor weight gain and whose developmental landmarks are retarded after three months of intensive medical therapy should also be selected for surgical repair. Infants with recurrent aspiration pneumonia secondary to gastroesophageal reflux should have prompt surgical repair if this distressing complication is not eliminated by medical therapy. Those with severe esophagitis are candidates for surgery unless major improvement is demonstrated after one month of medical therapy. A rare fifth indication for surgery is the distress of some families disrupted by the infant's vomiting to such an extent that parents beg for something to be done.

The European literature contains many more references[7,8,10,26,27] to hiatal hernia in infants and children than that emanating from the United States. It would seem that surgeons in England and in Europe are more apt to operate on babies with gastroesophageal reflux than those in North America. This may explain the large number of reports about this condition in the European literature. Not so easily explained is the marked difference in the incidence of esophageal stricture described in the European experience. Cahill and Waterston,[8,23,27] reporting from the Hospital for Sick Children in London, quote an incidence of stricture formation in infants and children with hiatal hernia as 31% from 1945 to 1954, increasing to 46% from 1954 to 1967. Carre[10] records an incidence of 21% collected from the European literature. Beix-Ochoa[6] reports 24% incidence. The frequency of esophagitis and stricture has been much less in our experience; the esophagitis has in most cases been mild to moderate, and we noted only one instance of stricture in an infant whose symptoms began before the age of one year.

The dearth of strictures reported in the American literature has been cited by some as evidence that gastroesophageal reflux is rare in the newborn. Those infants who respond to conservative treatment and in whom there is spontaneous clinical and radiological resolution of reflux by 18 months usually do not show late esophageal sequellae. However, this should not detract from the possible permanent nutritional effects of gastroesophageal reflux, particularly on the developing brain.

Of special note is the phenomenon of delayed gastric emptying, which was demonstrated in half the patients. The gastric delay was severe enough to require concomitant pyloroplasty in 15 of the 31 infants. This raises the possibility that a subtle form of pyloric obstruction may underlie the whole syndrome of gastroesophageal reflux in the infant. If such a hypothesis were proven, then the operative correction of gastroesophageal reflux in most babies would more appropriately be directed at widening the pylorus.

Late followup has been possible in 28 of these patients, and thus a good assessment of the results of the surgery could be made up to 8½ years after hiatal hernia repair. Results of a number of techniques for repair both by the abdominal and thoracic routes have been reported by Vos[25] (gastropexy), Bettex[4] (fundoplication), McNamara[19] (Mark IV of Belsey) and others.[5,8,16,24] These reports have shown the efficacy of each of these techniques in children. With vigorous diagnostic effort and scrupulous selection of patients, certain infants can be identified who are not responding to conservative therapy. These babies can be cured promptly by surgical means and saved from the deleterious effects of unremitting gastroesophageal reflux during this important early growth phase.

Conclusions

Gastroesophageal reflux in infants is manifested by: vomiting, failure to gain and grow normally, recurrent aspiration pneumonia and esophagitis.

In infants, fluoroscopic study of swallowed barium is the most reliable diagnostic method for demonstrating reflux.

There is no apparent derangement of gastric secretion in infants with symptomatic gastroesophageal reflux.

Medical treatment consisting primarily of propping the infant in the upright position controls the symptoms of gastroesophageal reflux in a large majority of babies so afflicted.

Although spontaneous resolution of gastroesophageal reflux occurs by 12 to 18 months of age in 85% of infants, certain debilitating effects in the early months of life connote failure of medical treatment.

In infants under one year of age, retardation of normal growth, recurrent aspiration pneumonia, and esophagitis are indications for surgical correction of gastroesophageal reflux when those symptoms are unrelieved by medical management.

Results of surgery to correct reflux in infants are highly satisfactory and, in this group of patients, unattended by serious complications or mortality.

Delayed gastric emptying has been noted preoperatively in 15 of these 31 patients. In these 15 patients a complementary pyloroplasty has been performed.

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DISCUSSION

DR. DALE JOHNSON (Salt Lake City): We were stimulated by Dr. Randolph's earlier presentation regarding this problem back in 1968, because we felt that we were not seeing the same spectrum of disease in infants and children. On looking closely, however, we discovered we were simply missing the problem.

In the past 2½ years we have performed studies on 36 children, pre- and postoperatively, who have required surgery for serious symptoms secondary to gastroesophageal reflux. Sixteen of these infants were under one year of age and correspond to the group Dr. Randolph has just presented.

For the most part, our experience has paralleled his, but we have studied our case material a little bit differently. We have performed esophageal motility, pressure, and pH studies, preoperatively and postoperatively, on our cases to see if we could measure the effectiveness of our surgery with these parameters.

The results have been interesting. We find that the pH-reflux test with tenth normal hydrochloric acid in the stomach and a pH probe in the lower thoracic esophagus is the most sensitive indicator of reflux and also the most reliable index of whether we have accomplished correction of the reflux postoperatively.

We agree that the Nisson fundoplication is an excellent operation to correct reflux. However, we also have had problems with the gas bloat syndrome in crying, sucking, air swallowing infants, and four infants with this operation have required nasogastric decompression for occasional gastric distention due to an overcompetent valve.

Our studies suggest that the Boerema procedure is effective, in contrast to the one case Dr. Randolph reported, if the Boerema is used for patients who do not have esophageal shortening or inflammatory changes due to reflux. We can correct the reflux, according to our postoperative pH-reflux test, and still provide capability for the child to vomit when necessary. Another advantage is that the procedure is simpler than the complete fundoplication.

We have not noted the same incidence of gastric outlet obstruction that Dr. Randolph commented upon, and we have not felt it necessary to perform pyloroplasty. Our radiologist has suggested there might be an antral web in four of our patients, and we actually opened the antrum in two of these, with negative findings. We subsequently have not opened the antrum, and we have not had postoperative problems from outlet obstruction.

(Slide) Finally, this shows the pre- and postoperative pressure relationships with the interesting finding that it is not necessary to change the pressure of the lower esophageal sphincter to accomplish the correction of reflux in infants and children.

It is also interesting that the pressure measurement of 5–8 mm in normal infants is lower than that for adults, and this high pressure zone stays at 5–8 mm even though complete correction of the reflux has been accomplished.

(Slide) This last slide confirms the material Dr. Randolph presented concerning post-surgical weight gain in children having failure to thrive. These cases are samples of our earlier experience. Two of these infants, referred after previous attempts at surgical correction of reflux, were within two pounds of birth weight at one year of age. They will be significantly retarded throughout their lives, and we feel this problem should be corrected before such long lasting damage has developed.

The pulmonary problems are also significant, and we feel that surgical correction is justified in infants with severe gastroesophageal reflux, whether or not a hiatal hernia can be demonstrated, providing the symptoms have not been relieved by vigorous positional therapy.

DR. THOMAS M. HOLDER (Kansas City, Missouri): I would like to call your attention to another symptom complex which may result from gastroesophageal reflux in infancy. We have recently seen four patients, age 2, 4, 8, and 22 weeks, who presented with respiratory arrest as a result of gastroesophageal reflux and aspiration. These were repeated episodes. Dr. Lucian Leape describes them as "dying spells." While that may not be technically accurate, it's descriptively correct, because these children have had complete cessation of respiration. They have had to be intubated and resuscitated. The episodes have been recurrent and have occurred in the hospital, in the nursery, and in the pediatric intensive care unit. They have been observed on several occasions.

The problem that this presents is that many physicians are not aware of this symptom complex and do not entertain the diagnosis of gastroesophageal reflux with aspiration. In addition, the patient often does not have overt vomiting, and, indeed, there may not be formula in the pharynx or in the trachea when it's aspirated. Finally, two of these four patients did not show reflux on their initial gastrointestinal studies. (The other two refluxed freely when first seen.) In one, the reflux was demonstrated on the second procedure, and in one on the third. In all four of the patients, their episodes of respiratory arrest ceased with treatment of their gastroesophageal reflux. This is another symptom of this disease which certainly should be treated. In addition, it may explain some of the crib deaths which have been thus far unexplained.

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): Relatively few pediatricians appreciate the significance of these observations. How many of these patients really end up with a fairly acute disease after a prolonged and morbid course of medicinal management when operation is really indicated?

I think perhaps the most useful of Dr. Randolph's contributions is that relative to how long one might persist with nonoperative treatment before operation is indicated. I think those of us who more commonly see individuals with hiatal hernia in a different age group, in a different setting, can appreciate the totally different clinical presentation of these patients, compared to the patients who come to see us with esophagitis, stricture formation, or otherwise. They are quite a bit different.

I would continue to suggest the usefulness of the fundoplication operation, of which we have now done a little over 300, only ten of which were in this particular age group. The construction of a loose but effective valve which is allowed to float within a broad range of anatomical patency about the esophagogastric junction will avoid much of the so-called gas bloat syndrome. It's a very infrequent observation in our adult patients, and in none of the ten children that we have seen has it presented any kind of clinically significant illness.

DR. EOIN ABERDEEN (Philadelphia): Our experience was that of the Thoracic Unit at the Hospital for Sick Children in London during the years 1960 to 1970. We saw more than a thousand children with hiatal hernia, and at that time found a curious difference from the United States. We were seeing many with this condition, and we wondered whether there was some true difference in geographical distribution or racial distribution.

The mystery has partly been solved, I think, by some surgeons who have taken a special interest in hiatal hernia, such as Dr. Randolph. They have found that there are more cases in the U.S.A. But maybe it is not just a problem of diagnosis. It has not been the practice for many of the radiological units in the children's hospitals in this country to pursue the diagnosis of hiatal hernia reflux, (and reflux is the crucial part), quite as vigorously, as is done in some European centers.

Of the more than 1000 cases which we treated, we operated on more than 200, and more than half of those had strictures before they were operated on.

Of those needing operation in the first year of life, in our earlier experience, using the Allison procedure, we found that the recurrence rates were uncomfortably high. So we reviewed the various operations available, and recognized that if holding a length of esophagus below the diaphragm is the crucial thing, there are, really two methods of achieving this. One is the plug-in-the-hole principle (the Belsey and the Nissen II operation). The other is the pull-down procedure in which the stomach can be fixed to the crus (Zeifert) to the median arcuate ligament (Hill), or to the anterior abdominal wall, (the Boerema operation). We found that the Boerema operation gave a longer segment of esophagus below the diaphragm in infants than the other operations. In 15 infants operated upon between 1963 and 1970, and chosen mainly because they had profuse vomiting—up to 15 times a day—there was prompt cessation of vomiting in every case and no recurrence.

Experience with the Boerema pull-down gastric fixation operation in older children involved at least a 12% recurrence late, but I won't confuse the treatment of the sick infants by discussing the problems of older children.

In our experience, an infant who is vomiting a lot and who has many respiratory problems can be very well managed by a simple operation of opening the abdomen (and in the infant you can do a small transverse incision just above the umbilicus) fixing the lesser curve to the anterior abdominal wall, and the process of closing the transverse incision (inaudible) helps to pull the gastroesophageal junction down even more.

The final answer is not yet available in the management of this condition, but Dr. Randolph's paper is a very important contribution.

DR. JUDSON G. RANDOLPH (Closing discussion): Dr. Aberdeen, we appreciate your telling us about this seeming disparity in the English literature and the American literature over the years. I'm very interested to hear of your success with the traction operation.

It was good to hear from Dr. Polk, with a broader perspective, pointing out the differences in the adult versus the infant in terms of symptomatology and presentation. Dr. Holder has very clearly described for us the diagnostic dilemma which so often occurs when a baby is languishing in the nursery, and the attending physicians are hovering around, without recognizing the simple mechanical problem which may lead to life threatening circumstances.

I wish to thank Dr. Johnson for his presentation of the pressure studies, which represents another dimension in evaluating these babies; another vote for the Boerema operation should not go unnoticed.

In closing, Dr. Boyden, I'd like to say that there are at least three questions which are left unanswered by this study: 1) Is the reflux a manifestation of some subtle, as yet ill-defined pathology at the pylorus? 2) what is the mechanism of spontaneous improvement of the reflux in babies treated conservatively? and 3) Do the infants who show reflux which spontaneously disappears on conservative management, represent those patients who will develop symptomatic hiatal hernia and reflux when they reach age 40?

If the answer to the last question is "yes," by the way, we'll start operating on all of those babies, and eliminate this condition in adults!

Management of Extrahepatic Portal Hypertension in Children

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Among 69 patients with PVT, 338 variceal bleeding episodes occurred. Only two patients died from bleeding, and both lived in remote communities and were inaccessible to medical care. Fifty-three children underwent 164 operations for the management of PVT. Once operative management was undertaken, subsequent operations frequently were necessary. Nonoperative measures controlled acute variceal hemorrhage in most instances during the past 10 years. Almost all patients who underwent splenectomy alone, variceal ligation, gastric division, splenic transposition, or makeshift shunts subsequently rebled. These operations are rarely indicated in the current management of children with PVT. Portal venography is essential to define the portal venous circulation before a shunt operation is attempted. Cavomesenteric or central splenorenal shunts prevented further bleeding in eight of 15 patients and are the most reliable operations to control bleeding in patients with PVT. Emergency operation is rarely necessary to control bleeding. Sixteen patients (average age 14.6 years) with PVT did not undergo any operations, and are alive. Each of the six patients with PVT who died from complications of portal hypertension did so within nine months of an operation. Four of these patients had previous splenectomy and died with sepsis as one of the major factors. Bleeding episodes became less frequent as the patients increased in age. Patients who underwent shunts under unfavorable circumstances or who received various other operations to treat portal hypertension appeared to have a higher risk of morbidity and mortality than those managed nonoperatively.

EXTRAHEPATIC portal venous thrombosis (PVT) has been recognized as the most frequent cause of portal hypertension in children, yet scant information has been recorded to indicate the long-term prognosis for patients with this condition. Since Clatworthy and associates[2–4] summarized the manifestations of PVT and recommended a logical course of management, most reports on this subject have emphasized clinical experience with various operations to decompress the portal venous circulation or to control variceal hemorrhage, with follow-up periods usually being short or unspecified.[6–9] The frequency of postoperative rebleeding and the increasing morbidity and mortality encountered with subsequent operations suggest that portal venous decompression may not be as straightforward an approach as initially believed. On the other hand, surprisingly little data have been published to indicate the clinical course of patients with PVT who have been treated by carefully planned nonoperative therapy. The optimal course of management for children with this condition, with a particular view toward long-term evaluation into adulthood, has therefore not been clearly defined.

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The combined experience of the UCLA Hospital and the Royal Children's Hospital of Melbourne, Australia, in the management of 69 children with PVT is summarized in this report. On the basis of this clinical experience, including several patients who were available for long-term followup observations, certain recommendations are made regarding the management of extrahepatic portal hypertension in children.

Clinical Material

During the 25-year period from 1948 to 1973, 15 children from the UCLA Hospital and 54 patients from the Royal Children's Hospital were treated for PVT. Thirty-eight of the children were male (55%) and 31 were female. Portal hypertension was first diagnosed under six years of age in 55 patients (80%) (Table 1). Fifteen

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TABLE 1. *Age at Which Extrahepatic Portal Hypertension First Diagnosed*

Age (Yrs.)	No. of Patients	
0–1	14	80%
1–3	23	
3–6	18	
6–10	6	
10–14	8	
Total	69	

children (22%) had a definite history of neonatal infection, most commonly peri-umbilical. No apparent association could be established between cannulation of the umbilical vein during the neonatal period and portal vein thrombosis. An episode of dehydration during early infancy occurred in several cases.

The most frequent initial clinical manifestation of portal hypertension was variceal bleeding, which occurred in 39 children (57%). Twenty-three of the remaining 30 patients in the study experienced variceal hemorrhage later in the course of their disease, most on more than one occasion. Seven children with PVT have never bled. Twenty-four patients had less than three bleeding episodes by the age of 16 years. None of the children died during the first episode of variceal hemorrhage. The average total number of bleeds per patient was 4.9; one patient experienced 24 separate episodes of hemorrhage. Transfusions were given during approximately one-third of the bleeding episodes, although it was rarely necessary to give more than one unit.

Symptomless splenomegaly was the second most common initial manifestation of PVT and occurred in 26 patients. Percutaneous splenoportography was performed on each of these patients to confirm the diagnosis and to determine the portal pressure. The liver was not enlarged, and the spleen was at least 2 cm below the costal margin in each of these patients. More than one-half of the patients had radiographically demonstrated esophageal varices; in 19 of these, variceal bleeding subsequently developed.

Ascites occurred in two young children with PVT; however, in both it was of mild degree, did not require specific therapy, and disappeared before the age of four years. Ascites was not used as an indication for operation in any of the patients. Mild ascites occasionally was observed as a postoperative complication after portal decompression. Anemia was the first manifestation of PVT in two infants.

Growth and development were normal in almost all the children with PVT, and most participated in physical activities to an equal extent as their peers between bleeding episodes. Splenomegaly was invariably present, although the size of the spleen varied considerably and, in general, enlarged as the patient increased in age with no relationship to the occurrence of variceal hemorrhage. Thirty-three children had evidence of hypersplenism as manifested by a leukocyte count of less than 2,000/mm^3 and a platelet count of less than 100,000/mm^3. In two patients from our early experience, the manifestations of hypersplenism were considered sufficiently severe to warrant a splenectomy in the absence of previous variceal bleeding. Both patients subsequently bled on many occasions.

Hepatomegaly did not occur in any of the patients in this study, and liver function tests were almost always within normal range. Liver biopsies were performed on the majority of the children, and the liver was histologically normal in each.

An esophagram was performed on almost all patients, and in approximately two-thirds, varices were demonstrated. This study was less helpful in children under four years of age. Diagnostic esophagoscopy was not performed on any of the patients. Percutaneous splenic portovenography under light general anesthesia was performed on 45 children. Operative mesenteric venography was performed on 16 children and provided good visualization of the portal venous system. This study was of particular value in delineating the location of veins suitable for shunting in patients who had previously undergone splenectomy. Indirect portography by means of selective celiac arterial contrast injection provided satisfactory visualization of the splenic and portal veins in several patients but, in general, was less satisfactory in defining the anatomy of the mesenteric venous system than was direct portography. Portal venous pressures were measured in all patients and values ranged 180–510 mm Hg (Table 2).

Treatment

Fifty-three children underwent 164 operations for the treatment of PVT; the average was 3.1. A variety of methods was used (Table 3). The average interval between the first hemorrhage and initial operative management was 1.7 years. Although 14 patients had only one operation, 12 had four or more operations, and one patient underwent 25 operations for the management of portal hypertension. The average number of bleeding episodes prior to operation was 3.6, and all but two

TABLE 2. *Portal Venous Pressure Measurements*

Pressure (mm H_2O)	No. of Patients
Under 200	7
200–300	27
300–400	22
400–500	9
Over 500	4
Total	69

TABLE 3. *Operations for 53 Patients with PVT*

Operation	No. of procedures*	No. Rebled	No. Reoperated	No. Died
Splenectomy alone	20	19	17	1
Variceal ligation	22	22	20	2
Variceal injection	1	1	1	0
Gastric division	17	15	10	3
Gastrectomy with colon interposition	2	1	1	0
Cavomesenteric shunt	9	4	3	0
Splenorenal shunt	6	3	1	0
Makeshift shunt	6	6	4	0
Splenic transposition	3	2	1	0
	86	73	58	6

* Several patients had more than one of the operations listed. Seventy-eight additional operations were performed on the 53 patients, including lysis of adhesions, revision of anastomosis, gastrostomy, drainage of abscess, etc.

patients had experienced at least one hemorrhage. Once operative management was undertaken, subsequent operations were frequently necessary (average 2.1 per patient), and the morbidity was high. Esophageal balloon tamponade was employed in several children, as was systemic vasopressin. The data suggest that tamponade has been of considerable value, but there does not appear to be any convincing evidence of the value of vasopressin in this series. Nonoperative measures, including hospitalization, bed rest, sedation, vitamin K administration, oral antacids, and withholding of oral feedings were successful in stopping the acute variceal hemorrhage, within 48 hours in most instances. Bleeding episodes frequently followed the onset of an upper respiratory tract infection.

Nineteen of 20 children who underwent splenectomy alone as the initial operation rebled, although the next bleeding episode was delayed an average of 3.4 years. Seventeen of these patients underwent further operations, and one died. Many additional patients underwent splenectomy at the time of other operative procedures.

Twenty-two patients underwent variceal ligation for acute bleeding, but subsequent bleeding occurred in all, and two patients died.

Esophagoscopy with transesophageal injection of the varices with sclerosing solution was performed on one child during an acute bleeding episode; however, further hemorrhage occurred one month later.

Porta-azygous disconnection and gastric division (Tanner procedure) was performed on 17 children; rebleeding occurred in 15, three of whom died.

Two patients underwent esophagogastrectomy; one experienced subsequent rebleeding, and the other underwent multiple operations to relieve obstruction of the interposed colon segment. Neither of these patients died after esophagogastrectomy. One patient who underwent vagotomy and pyloroplasty after four previous operations developed recurrent bleeding and has experienced symptoms compatible with the dumping syndrome.

Shunting operations were performed in 21 children and were the most successful of the operations performed to prevent bleeding. End-to-side cavomesenteric anastomoses were performed in nine patients, and four have experienced further hemorrhage. Six patients underwent central splenorenal anastomosis, and three patients rebled. In one of these patients the shunt thrombosis produced complete occlusion of the renal vein as well. Makeshift shunts were performed on six children, and each patient experienced recurrent bleeding shortly thereafter. Cavomesenteric shunts produced the greatest decreases in portal pressure. Each of the shunts that did not decrease the portal pressure more than 120 mm H_2O subsequently became thrombosed, and recurrent bleeding ensued.

Surgical transposition of the spleen into the left chest was performed in three children, two of whom have experienced subsequent variceal hemorrhage.

Sixteen (23%) of the children in the present study did not undergo any operations for treatment of portal hypertension, and all are still alive except for one child who was killed in a railroad accident of causes unrelated to the portal hypertension. An average of 2.4 episodes of variceal hemorrhage occurred in these patients. Portal pressures were measured in all but one of the 16 patients, and the average pressure was 317 mm H_2O. In comparison, the average portal pressure recorded in the 21 patients at the time of portal-to-systemic shunting was 303 mm H_2O. The current average age of this group of nonoperated patients is 14.9 years, ranging 4–23 years, and is only six years younger than that for patients who have undergone operations (21.2 years).

Current followup information is available on 51 patients whose ages range 3–58 years (average 21.6 years). Recent information was not available for 11 patients; however, the average followup available for this group of patients beyond the time when portal hypertension was first diagnosed is 12.9 years. Bleeding episodes became much less frequent after the age of 16 years; only seven of 29 patients have bled beyond this age, and four of these have required operative treatment.

Only seven patients in this study died, and of these one was killed in a railroad accident (Table 4). The six deaths all occurred in the group of 53 children who underwent operations: one of 20 children died after splenectomy alone (5%); two of 22 died after variceal ligation (9%); and three of 17 died after porta-azygous disconnection (18%). No child died after a shunt operation. All 6 children died within 9 months of an operation.

Discussion

The manifestations of portal hypertension attributable to extrahepatic venous obstruction in children have been reviewed previously,[2–4] and the common findings of variceal bleeding, splenomegaly, anemia, melena, and varying degrees of hypersplenism were observed in almost all patients in the present study. In contrast to the experience of Clatworthy and Boles,[3] ascites was rarely seen. None of the patients had concomitant peptic ulcers.

Portal vein thrombosis is primarily a mechanical problem, with hemorrhage as the only major risk to the patient. In contrast to the high mortality for patients with intrahepatic disease who experience variceal bleeding, the mortality rate is extremely low for patients with PVT, as observed by other authors.[1,11] As noted previously,[10] no direct correlation could be established between the portal venous pressure and the frequency or severity of bleeding episodes. There were 338 episodes of bleeding among the 69 patients in this study. Only two patients died as a direct result of bleeding, and both these patients lived in remote communities and did not receive acute medical care while bleeding. Bleeding episodes were heralded by an upper respiratory tract infection more than 70% of the time. Parents were advised to be particularly observant for melena during such infections. One child experienced 16 bleeding episodes before the age of five years, each related to a recurrence of pneumonitis associated with a broncho-pleural fistula following pulmonary lobectomy for lobar emphysema; bleeding episodes became sparse after the fistula closed. Several patients experienced bleeding episodes after ingestion of aspirin, some of which were the most severe bleeds encountered; thus, parents have been advised to refrain from giving this medication. Bleeding episodes were generally more severe when they occurred following operations to relieve portal hypertension than in patients who had not been operated upon.

Emergency operations for bleeding from PVT have been performed rarely during the past 10 years. Most variceal ligation procedures were performed prior to that time, and the reason for operation in many of these patients was not apparent. This procedure was rarely done as the initial operation, and in no patient was it performed for less than three bleeds. In general, we agree with the view of Shaldon and Sherlock[11] that the variceal hemorrhage can be controlled by nonoperative methods; however, a few children have bleeding that is so persistent and catastrophic as to require balloon tamponade, intra-arterial pitressin infusion, variceal ligation, or gastric division, despite the fact that further bleeding has followed all such operations in our experience. No emergency shunts were performed in this series.

In all but two patients, splenectomy alone eventually was followed by recurrent hemorrhage that made difficult the assessment of the portal venous system prior to a later operation. Splenomegaly *per se* has rarely been a problem, and no case of splenic rupture has been encountered, despite a lack of restrictions on physical activity. Of particular note is the fact that four of the seven children who died had undergone a previous splenectomy, and each died with sepsis, one from pneumococcal infection. Our experience would substantiate previous reports that recommend that splenectomy alone for bleeding or for hypersplenism has no place in the management of PVT, particularly in the young child. On the other hand, splenectomy may facilitate construction of a portal-systemic venous shunt in older children and may reduce abdominal swelling, thus enabling return to normal physical activities.

In seven of the 15 patients with cavomesenteric and splenorenal shunts, thrombosis and rebleeding occurred.

TABLE 4. *Cause of Death in Patients with PVT*

	Operations	Complications	Age at Death*
1.	Variceal ligation and Splenectomy	Gastric perforation; sepsis	9 yrs.
2.	Splenectomy alone	Pneumococcal meningitis; sepsis; variceal hemorrhage	14 mos.
3.	Gastric division (Tanner procedure)	Died from hemorrhage in remote community	18 mos.
4.	Gastric division and Splenectomy	Gastric fistula; sepsis	23 yrs.
5.	(1) Splenectomy alone (2) Variceal ligation	Subphrenic abscess; pneumonia; sepsis; jaundice	8½ yrs.
6.	Gastric division and Splenectomy	Died from hemorrhage in remote community	15 mos.
7.	No operation	Killed in railroad accident; No complications related to PVT	12 yrs.

* Each patient died within 9 months of an operation.

Six additional patients had makeshift shunts, and each has rebled. End-to-side cavomesenteric shunts were the most successful in preventing rebleeding, although the long-term benefits were unreliable, particularly when performed in patients under the age of six years. In several patients, the thrombotic process occluding the portal vein extended into the splenic and mesenteric veins, making surgical decompression difficult. In one such patient the renal vein thrombosed after a splenorenal shunt. We concur with Clatworthy[5] and others that a shunt with a diameter of less than 1 cm is unlikely to remain patent and that shunt procedures should be deferred until the patient is eight years of age. In the rare patient with PVT that extends to the proximal splenic vein, the Warren distal splenorenal shunt may be helpful.

Progressive portal hypertension in children with PVT is usually associated with an increase in the splanchnic-systemic venous collateral circulation.[12] Variceal hemorrhage is usually the result of an insufficiency of these collaterals,[10] and repeated intra-abdominal operations are likely to disrupt many of these collateral channels. One must, therefore, weigh the probability that a large shunt can be established that will remain patent against the chances that the collateral circulation might be divided in vascular adhesions or that injury to other structures might be produced. A large number of patients in this series have experienced postoperative complications, including ascites, intestinal obstruction, wound infection, intestinal perforation, hemorrhage, and jaundice. One patient sustained an injury to the common bile duct during construction of a shunt at 3 years of age, and severe cirrhosis and jaundice subsequently developed. The condition was relieved several years later with a left hepatico Roux-en-Y jejunostomy. Seventy-eight operations were performed to treat complications of previous operations other than bleeding.

Concern regarding the long-term effects of portal-systemic shunts for PVT has been expressed by Voorhees and associates[13,14] who found that in five of eight patients with patent shunts who were followed beyond the age of 20 years, emotional disorders and abnormal electroencephalograms developed. A few of the shunted patients in the present study were emotionally unstable, but this was attributed to the effects of prolonged hospitalization and repeated operations, and we have no documented evidence of abnormalities of the central nervous system.

The experience from this study suggests that a few children with PVT may be managed very satisfactorily and safely without operation despite recurrent variceal bleeding. Bleeding episodes generally became less frequent as the patients increased in age and became less susceptible to respiratory infections. When bleeding continues to recur with moderate frequency, a planned portal-to-systemic venous shunt would seem justified, provided that a shunt with a diameter of more than 1 cm can be constructed. Portal venography is very helpful in making this decision. Patients who undergo shunts under less favorable circumstances and those who receive various other operations to treat portal hypertension appear to have a higher risk of morbidity and mortality than do those managed nonoperatively. There was no significant difference in the incidence of hemorrhage in nonoperated patients as compared to operated patients in this series, with followup extending into late adolescence.

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DISCUSSION

DR. H. WILLIAM CLATWORTHY, JR. (Columbus, Ohio): This paper gives us some insight in a reasonable number of cases—sixteen—into the natural history of this disease; and this information really has been very hard to glean from the previous literature.

I feel these children with extrahepatic portal bed block must be individualized from the beginning; that some will prove to be shuntable early and have good veins of a suitable size and that some type of mesocaval or central splenorenal, or perhaps retropancreatic shunt, will solve their plumbing problems for the rest of their lives because they have good livers, even though they have bad veins.

There's a large group, as we accumulate our data, that really have such bad veins, or are of such an unsuitable size to work with, that the shunt failure rate is very high; and perhaps, in our wisdom in the future, we will be better able to select cases for surgery.

I would like to introduce a few facts in support of what you have already heard. Dr. Child asked me to review this subject for a book a little while ago (Major Problems in Clinical Surgery, Philadelphia, W. B. Saunders, pp. 243–66, Jan. 1974), and I was able to find 418 cases of extrahepatic block reported in the literature. There were 53 deaths (12%), which compares closely with the 10% in this series. Twenty-three of these review cases (5%) died of hemorrhage; 22 (5%) died from operations, and 8 (2%) died of hepatitis, which may be presumed to be associated with repeated blood transfusions.

Our own series of shunts (slide) is also very similar. In 36 cases we have done 21 shunts. We have had eight direct attacks initially on the varices. We only have four as an unoperated control group, and we have three treated by splenectomy alone.

As for shunts, we have had 12 successes and nine failures who re-bled. Our series goes back to 1953 and has been followed up to 21 years.

I do think we are becoming more conservative. We now have a number of children we're following. We feel we should not give up shunts, though, because this procedure cures the patient—if it's done on the proper patient.

Dr. John Hoskins Foster (Nashville, Tennessee): Our experience has been somewhat similar to Dr. Clatworthy's and Dr. Fonkalsrud's. Since 1950, we have followed 21 children with extrahepatic portal vein obstruction, all of whom have had surgical treatment. There were three deaths. Two were patients who were treated by splenectomy alone, prior to 1952. The other death was a young boy who had undergone a prolonged laparotomy in attempt to find a vein and create a makeshift shunt. The procedure finally had to be abandoned. He died in the early postoperative period.

We had some of our shunts in children under five years of age thrombose in the '50s, and at that time adopted a policy of not doing a shunt until we are confident that the vein is big enough for a successful mesocaval or central splenorenal. This has usually been at age nine or ten years.

Seventeen children had a portal-systemic shunt and one had transposition of the spleen into the left hemithorax. Four children who underwent a splenorenal shunt in the 1950s and had thrombosis of the shunt have subsequently undergone a successful mesocaval shunt. These 18 children are living and well. The 17 shunts are patent.

Certainly you can manage these patients conservatively, and they will stop bleeding, and this is why we are able to manage these children by non-operative means until they are big enough for a successful shunt. The question posed by Dr. Fonkalsrud is "why not treat these children by non-operative measures if it can be done successfully?" In my opinion the answer is that it is not wise to continue each year to give these children three to six units of blood indefinitely.

Dr. Jeremiah G. Turcotte (Ann Arbor): Dr. Fonkalsrud has provided us with an important contribution by describing the natural history of extrahepatic portal hypertension in children without the confusion introduced by operative intervention. His description is not quite nature in the raw, but nature aided and abetted by skilled physicians and many blood transfusions.

We agree with the conclusions of this report, but might give a bit different emphasis to the interpretation of the data, based on our own experience. In the last few years we have reported our experience with two groups of patients with extrahepatic portal hypertension. One analysis concerned patients in which the diagnosis of extrahepatic portal hypertension was first made in adults, the average age being about 50 years (Am. J. Surg., 123: 35–42, 1972). We found, to our surprise, that with an average followup of four years that all patients who survived operation were alive, whether or not we had been successful in constructing a portosystemic shunt. The only patients who died were two in whom a portosystemic shunt was not constructed after an extensive intra-abdominal hemorrhage and who continued to bleed in the postoperative period. In this group of patients thrombosis of the portal system tends to be more extensive than in children and a preoperative mesenteric angiogram is essential to determine if an adequate splanchnic vein is available before embarking on an operation.

The second review we published concerned extrahepatic portal hypertension in children (Arch. Surg., 98:451–456, 1969). In our experience, some children continue to bleed frequently and massively even if they have not had previous operations. Others develop massive splenomegaly and become symptomatic with this. We certainly would agree that probably not all children need to have shunts constructed, but the clinical course of some patients will be such that a shunt is indicated.

Finally we became interested in the long-term results of children undergoing mesocaval shunts (Am. J. Surg., 127: 19–24, 1974). All these children were under 16 and most were under ten years of age at the time of construction of the shunt. Eleven had thrombosis of the portal vein. Two children thrombosed their shunts in their early postoperative period, but the others have remained open for as long as ten years with no long-term morbidity. Therefore, on the basis of our experience we would recommend that in carefully selected patients mesocaval shunts be constructed for children under the age of 13.

Dr. William P. Mikkelsen (Los Angeles): As patients grow older, and as they pass the age of 20, they seem to stop bleeding and in a few of these the varices disappear.

In the successfully shunted child, as the years go on, BSP retention steadily increases, and some of these children have a fetor hepaticus. I just wonder, when they have been followed long enough, whether they may develop encephalopathy later on in life.

Dr. Thomas V. Santulli (New York): I think this is an extremely important paper which parallels the experience as reported by Dr. Voorhees of our institution, Babies Hospital of Columbia-Presbyterian Medical Center.

There are two observations I would make. One is that emergency shunting is almost never done any longer in our institution since we have contradicted aspirin in the treatment of all these children that we know suffer with the disease, and since we have very heavily sedated our children who are admitted for rebleeds. They are sedated, almost asleep, around the clock, and the hemorrhage usually stops.

Secondly, as has been mentioned by the last discussant, in our long-term followup in these children, with no matter what type of shunt procedure, the very high incidence of encephalopathy and neuropsychiatric abnormalities has been most discouraging. Indeed, it is almost 100% if the followup is long enough.

Dr. Charles Gardner Child, III (Ann Arbor): All of Guido Banti's original publications emphasized that splenomegaly, anemia, and leukopenia occurred in young people who went on to die many years later of some kind of liver disease. Curiously enough Banti never recognized bleeding from esophageal varices as part of the syndrome which bears his name. He clearly recognized, however, that if patients with Banti's disease were followed long enough they died of liver failure.

I am aware of Dr. Arthur B. Voorhees discouraging report of children followed up to 20 years after portal decompression. Many of these ultimately developed severe emotional and neurological disturbances. At Michigan we cannot duplicate this experience but then our patients have not been followed for long periods of time.

There are still many aspects of portal thrombosis that are not well understood today and many of these may only be clarified after we follow our patients for as long as Banti did and as long as Dr. Voorhees and Dr. Fonkalsrud are now doing.

Dr. Eric W. Fonkalsrud (Closing discussion): Dr. Clatworthy, who has contributed perhaps more than anyone else to our general knowledge concerning extrahepatic portal venous obstruction, has highlighted several important points in the management of patients with this condition. Of major importance is the point that the surgeon should not feel obligated to do a shunt or other major operative procedure when in the abdomen of a child with portal vein thrombosis. Shunts should only be performed when the anatomy has been clearly defined and has been demonstrated to be favorable. It is probably better to close the abdomen without attempting to perform makeshift shunts or shunts that are small. We were quite surprised to find that 78 of the 164 operations performed on the patients in our clinical review were performed to correct problems created by previous operations. Our clinical review would substantiate Dr. Clatworthy's point that a shunt performed in a child should be large enough to remain patent for many years; it appears that a 1 cm diameter shunt is the minimum size that will remain patent under most circumstances. It is rare that a child under 8 years of age with portal vein thrombosis will have mesenteric or splenic veins of sufficient size to perform a successful shunt, and our experience would reemphasize the view that shunts or other portal decompressive operations should rarely be attempted on children under 8 years of age. The pressure gradient between the portal vein and the vena cava has only a slight influence on the likelihood of a small shunt remaining patent.

It is our view that children with extrahepatic portal obstruction should be followed by surgeons and pediatricians together since the decision regarding whether or not an operation is to be performed must be weighed on the basis of many factors, however, in the end the decision is up to the surgeon, much as is the case in the management of a patient with a bleeding ulcer.

I would like to thank Drs. Foster, Turcotte, Mikkelsen, Santulli, and Child for their many comments and for relating their experiences to us. Both Dr. Mikkelsen and Dr. Santulli have indicated their experiences with the development of encephalopathy in children who are shunted for extrahepatic portal venous thrombosis despite the presence of normal livers. Although a few of our patients are now in their third and fourth decades of life following shunting operations in childhood, we have not yet identified a patient who has experienced true encephalopathy, although a more careful review and followup of our shunted patients will be performed. The reasons for developing encephalopathy are not entirely clear, and further information and clinical experience on this subject should be forthcoming.

Lastly, I would like to stress that emergency operations are rarely if ever indicated for extrahepatic portal venous thrombosis in children. Acute variceal bleeding may be stopped without operation in most cases using techniques currently available, thereby permitting a planned operation to be performed at a suitable age to correct the problem.

Urinary Tract Refunctionalization After Prior Diversion in Children

W. HARDY HENDREN, M.D.

From The Division of Pediatric Surgery, Massachusetts General Hospital and Department of Surgery, Harvard Medical School, Boston, Massachusetts

Thirty-two children who had undergone previous urinary diversion were operated upon to refunctionalize the bladder. In 24 the diversion had been considered permanent, and in eight, temporary. Success in these procedures suggests that many young patients deserve a second look for possible "undiversion."

SEVERE OBSTRUCTIVE UROPATHY is a common problem in infants and children and is often one of the most difficult with which the surgeon must contend. In recent years there has been increased effort directed toward primary repair in these cases,[2,3,12–15] however, many children have been treated by either permanent or temporary urinary diversion.[5,16,17,19,22,23,25,26] Diversion techniques have included ileal loop or conduit, cutaneous vesicostomy, suprapubic tube cystostomy, end or loop cutaneous ureterostomy, and tube nephrostomy. Although such a diversion can be life saving, particularly in young infants with uremia, the quality of life leaves much to be desired if the urine is diverted. Further in many instances in our experience there is often low grade chronic bacilluria in some cases diverted by any of the above techniques. Most noteworthy is the increasing amount of data underscoring the long term complications in urinary tracts diverted by ileal conduit.[3,27] These complications likely result in most instances from free reflux in these conduits favoring growth of bacteria and formation of stones.

Improved results of reconstructive pediatric urologic surgery has prompted an attempt to refunctionalize the lower urinary tract in certain children who had undergone a prior diversion procedure. As shown in Fig. 1, 32 patients have been operated in the past five years. Thirty of these patients had undergone their urinary diversion elsewhere and were referred for "undiversion"; in two instances (cases 1 & 2) the diversions had been done by us prior to the era in which we began performing a primary reconstruction in babies.[12] In 24 cases the diversion had been considered permanent, and temporary in 8. Age at operation varied from 2 months to 18 years, with an average of 7.5 years. The duration of urinary diversion averaged seven years among the "permanent cases," and 2.8 years for the "temporary" ones. There were 5 girls and 27 boys. Obstructive pathology in these youngsters included 17 urethral valves, 5 cases with the "prune belly" syndrome, 3 with ureterocele, and 1 with ureteropelvic junction obstruction. Three had imperforate anus.

As shown in Fig. 2, 10 of the 32 children had only one functioning kidney. The 24 permanent diversions included: 10 ileal loop; 5 end ureterostomy; 3 loop ureterostomy; 3 nephrostomy; 3 cystostomy. Among the 8 children for whom a temporary diversion had been performed as an initial decompressive procedure, with the view toward ultimate reconstruction, there were 7 with loop ureterostomy and 1 with nephrostomy.

The bladder in these children was usually very small from long standing disuse, which precludes satisfactory preoperative assessment except to note sensation when filled. In each of these cases, however, the bladder stretched up to satisfactory capacity several weeks post operatively, even when it was a 15–20 cc contracted, fibrotic structure at operation. In 30 patients reported from The Hospital for Sick Children, Great Ormond Street, London,[18] 7 had contracted, non-distensible bladders. Tanagho[29] reported 28 patients with temporary diversion, of whom 4 had contracted bladders, 3

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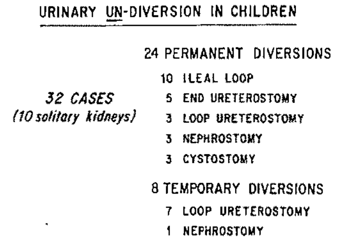


URINARY UN-DIVERSION IN CHILDREN

32 CASES
(10 solitary kidneys)

24 PERMANENT DIVERSIONS
- 10 ILEAL LOOP
- 5 END URETEROSTOMY
- 3 LOOP URETEROSTOMY
- 3 NEPHROSTOMY
- 3 CYSTOSTOMY

8 TEMPORARY DIVERSIONS
- 7 LOOP URETEROSTOMY
- 1 NEPHROSTOMY

FIG. 1. Types of prior urinary diversion.

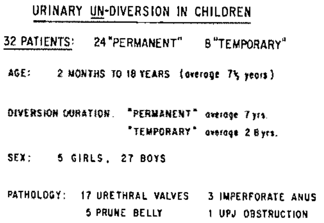
requiring reinstitution of diversion. He stressed, therefore, that supravesical diversion should be used for the shortest time possible.

It has been our experience that each of these cases differs in some respects from every other one. This paper will present 13 case examples which will illustrate most of the problems encountered in the overall group of 32 children. Some of them have been included in two prior reports on this subject.[6,9]

Undiversion Following Prior Ileal Loop

There were 10 children who had undergone an ileal loop diversion as a life-long measure. It is this group which has posed the most interesting technical challenge in reconnecting the upper tract to the bladder in a manner to provide free drainage yet not allow reflux. In Fig. 3 is shown a common anatomic situation seen in youngsters who have undergone permanent ileal conduit diversion for lower obstructive uropathy. The bladder is generally small from disuse, and its wall is often, although not always, thick-walled from hypertrophy caused by the original obstructive pathology, most often urethral valves in this series.

Use of small bowel as a ureteral substitute is not new. In a review of this subject and a report of 4 cases from U.C.L.A. Medical Center,[20] it was noted that the technique was first proposed in 1894. Goodwin *et al.*[8] reported use of this procedure in 16 patients, in a variety of anatomic relationships. They did not taper the caliber of bowel as Swenson did,[28] nor was an antirefluxing anastomosis used; they emphasized joining the conduit low in a fixed part of the bladder to avoid angulation during filling. Baum[1] felt that a large anastomosis of ileum to bladder was important to assure free drainage, accepting reflux as a consequence. In 10 patients reported by Prout *et al.*[24] there was reflux in 9. Many of the patients reported have been adults with normal bladders. In children with thick walled, hypertrophied, small capacity bladders we have preferred to perform an antireflux procedure although it is technically more difficult. The caliber of the conduit is tapered about 50% to enhance peristaltic emptying, to reduce its absorptive surface, and to allow a non-refluxing reimplant. From extensive experience with vesicoureteral reflux we believe that an antirefluxing method must be preferred to one which permits reflux, particularly in young patients who have already often considerable renal damage.



URINARY UN-DIVERSION IN CHILDREN

32 PATIENTS:	24 "PERMANENT"	8 "TEMPORARY"
AGE:	2 MONTHS TO 18 YEARS (average 7½ years)	
DIVERSION DURATION.	"PERMANENT" average 7 yrs. "TEMPORARY" average 2.8 yrs.	
SEX:	5 GIRLS, 27 BOYS	
PATHOLOGY:	17 URETHRAL VALVES 5 PRUNE BELLY 3 URETEROCELE	3 IMPERFORATE ANUS 1 UPJ OBSTRUCTION 3 MISCELLANEOUS

FIG. 2. Data on 32 patients.

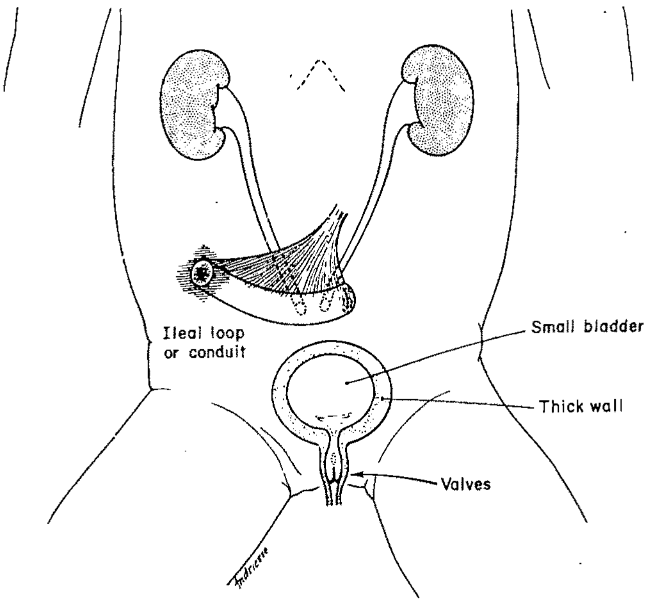


FIG. 3. Most common anatomy with ileal conduit diversion.

In Fig. 4 are shown the various means which can be used in undiverting one of these cases. Rarely are both ureters long enough to achieve a straight forward ureteral reimplantation. In addition, the bladder may be too small to permit two satisfactory reimplantations, in which case it is preferred to reimplant the better ureter in combination with transureteroureterostomy of the opposite one. Commonly both ureters are too short to reach the bladder, and the conduit must be used. Autotransplantation of a kidney downward is another possible solution, but we have preferred to avoid that method in patients whose kidneys are already generally quite abnormal. In two of our patients (Cases 2 & 3) there was a pyeloileal conduit with no ureter remaining. In Fig. 5 is shown the technique used for implanting an ileal conduit into the bladder in 6 of the 10 cases previously diverted by ileal conduit.

Case Reports

Case 1. (Fig. 6) This patient was referred as a newborn in 1963 with distended bladder and bilateral hydronephrosis caused by a large ureterocele with a duplex system on the left. Although

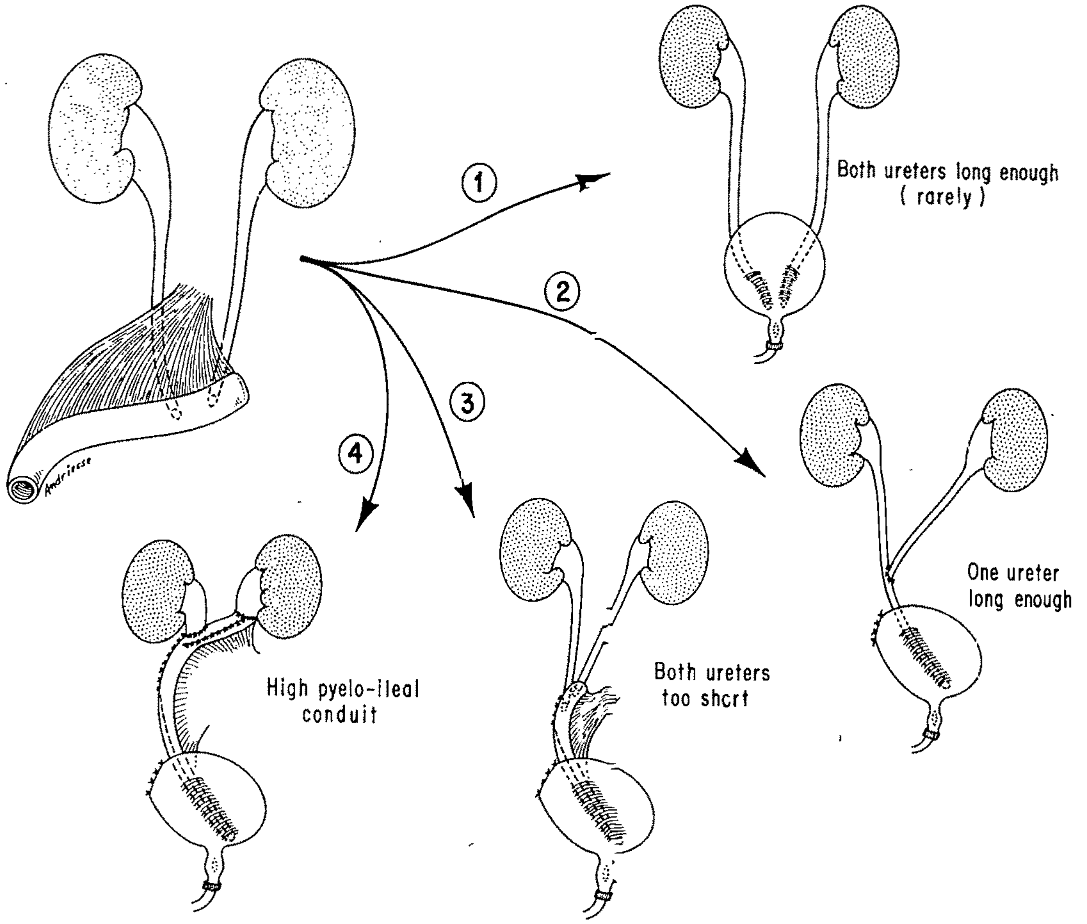


FIG. 4. Alternative reconstructive techniques following ileal loop.

today a direct reconstructive procedure would be performed[10] several lesser measures were done. They included unroofing the ureterocele, Y-V plasty to the bladder neck, and upper pole nephroureterectomy. The patient did poorly and a pyeloileal conduit was performed at age four months. The stump of right ureter was spared in case it might be of use in the future (Fig. 3a). The patient thrived but required continuous antimicrobial therapy for bacilluria. The intravenous pyelogram at age 6 (6b) showed satisfactory renal cortex and function on the right, but a contracted left kidney. At age 6 years, in July of 1969, reconstruction was performed (6c), removing the nubbin of left kidney and that part of the conduit joining it to the right side. The conduit was tapered and used to bridge the gap between the right renal pelvis and the stump of ureter remaining. A temporary nephrostomy was used for two weeks; antegrade study before its removal (6d) showed a satisfactory result. Current intravenous pyelogram, five years postoperatively, is shown in 6e. The patient is completely well (6f).

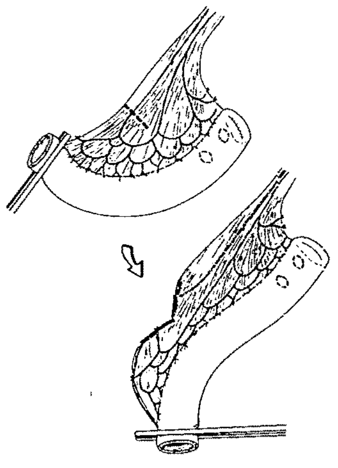


FIG. 5a. Mesentery is opened to straighten conduit.

Comment

The tapered bowel segment is functioning well as an upper ureter. Her reconstruction was made easier by using the lower ureter which had been spared, but in most cases the lower ureter has not been useable because it was either refluxing or obstructed, which was not the case in this patient.

Case 2. (Fig. 7) This patient was referred at age 2 weeks with uremia and hyaline membrane disease; suprapubic cystotomy had been performed previously. Creatinine clearance was only 2 L absolute. At the age of one month bilateral end cutaneous ureterostomy was performed, but he did poorly, and at two months of age a pyeloileal conduit was constructed (Fig. 7a, b). Surprisingly he thrived during the ensuing six years and had stable renal function (BUN 32 mg.%, creatinine 1.2 mg%, and creatinine clearance of 24 liters per day absolute). At age 6 years, November 1969, the ileal loop was joined to the bladder (Fig. 7c). Type I urethral valves were destroyed endoscopically. The bladder wall

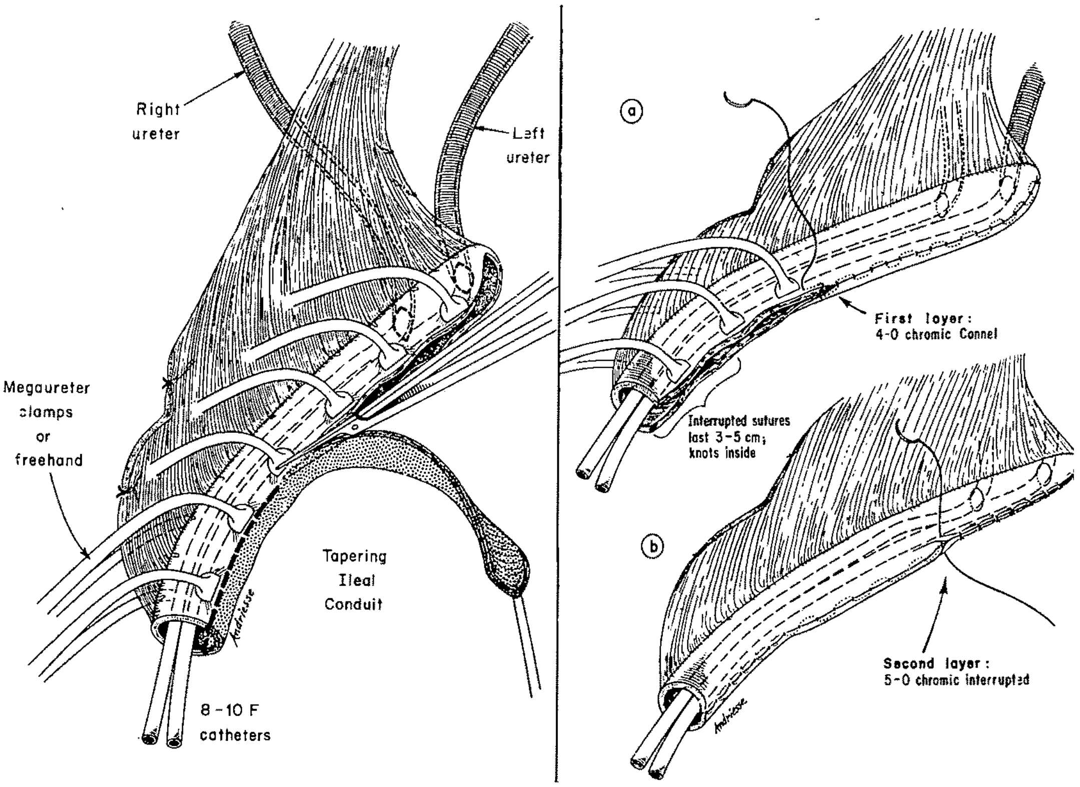

Right ureter
Left ureter
Megaureter clamps or freehand
Tapering Ileal Conduit
8-10 F catheters
Andriesse
ⓐ
First layer: 4-0 chromic Connel
Interrupted sutures last 3-5 cm; knots inside
ⓑ
Second layer: 5-0 chromic interrupted
Andriesse

FIG. 5b. (Left) Caliber is tapered. FIG. 5c. (Right). Two layer closure with chromic catgut. Distal part of closure with interrupted sutures in order to be able to trim conduit later to suitable length.

was still hypertrophied, although it had been defunctioned for six years. The distal half of the conduit was tapered by about 50% of its diameter and a tunnelling reimplantation was performed into the bladder, together with Y-V plasty of the bladder neck. A drainage catheter was left in the loop from below for two weeks. A retrograde study two months post operatively (Fig. 7d) showed satisfactory caliber of the tapered conduit. Cystogram initially showed a small amount of reflux from the bladder during voiding into the lower part of the conduit, but later study showed no reflux. The patient thrived, was free of urinary infection, and function remained stable. Fluoroscopic evaluation of conduit emptying was performed by antegrade injection of dye with a percutaneous needle through the left flank. The lower tapered segment of the conduit propelled dye effectively into the bladder; the untapered segment of the conduit between the left and right kidneys showed active peristalsis, but churning of the dye in that part of the conduit in contrast to effective emptying of the tapered section of the conduit. Therefore at age 8 years, August 1971, the upper conduit was tapered to reduce its caliber to see if this might improve peristaltic emptying, and whether by decreasing the absorptive surface of bowel there might be an increase in renal function. This resulted in an increase in average values of creatinine clearance from 24 L/day absolute to 38 L/day absolute. Antegrade injection of dye into the left kidney showed (Fig. 7e) active transport to the bladder. Pressure in the left renal pelvis was normal, 8 centimeters of water. The patient is well (Fig. 7f) now almost five years following "undiversion."

Comment

There are many children like this lad who have undergone high pyeloileal conduit for such severe obstructive uropathy that reconstructive surgery was not thought feasible in prior years. Although this boy has severe hydroneprhosis, with diminished renal function, he has fared extremely well after redirecting his urine into the bladder. There has been no loss of renal function, the urine has been consistently sterile, and his life style has been improved immeasurably. Renal transplantation in

FIG. 5d. Bowel tapering completed, to about 50% of initial diameter. It must not be too small.

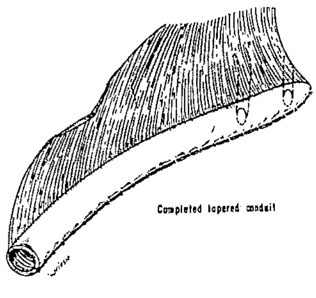
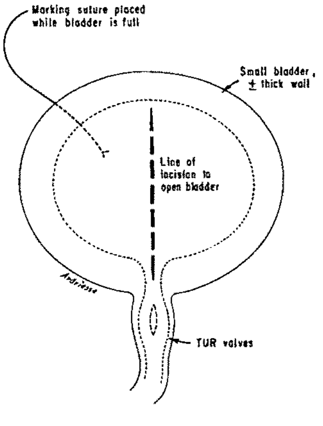


FIG. 5e. A suitable point for entry of the tapered bowel conduit is selected while the bladder is full, taking care to make it posteriorly, not in the side wall or dome of the bladder where it can angulate when the bladder is filled.


Marking suture placed while bladder is full
Small bladder, ± thick wall
Line of incision to open bladder
Andriesse
TUR valves

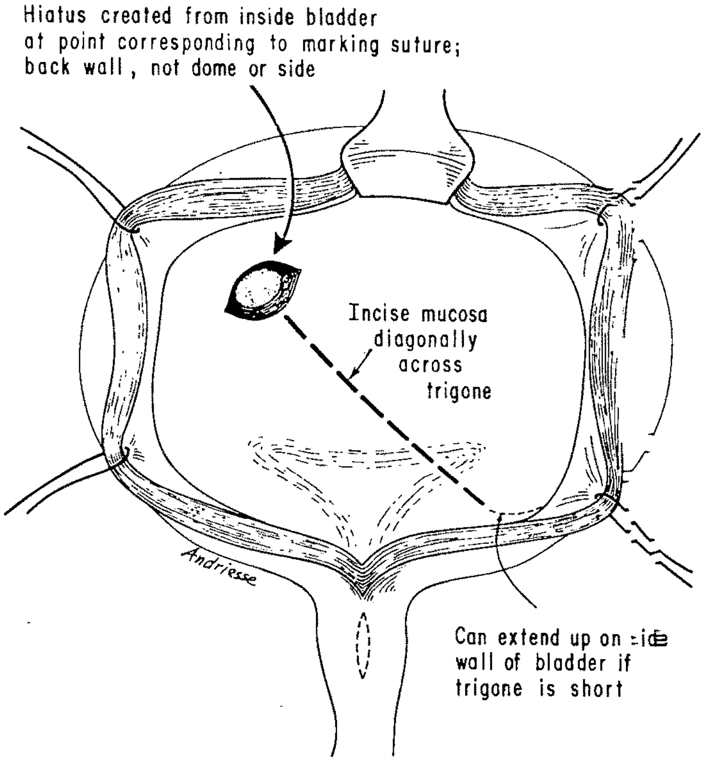

Hiatus created from inside bladder
at point corresponding to marking suture;
back wall, not dome or side
Incise mucosa
diagonally
across
trigone
Andriesse
Can extend up on side
wall of bladder if
trigone is short

FIG. 5f. The mucosal tunnel is created by incising mucosa to make a tunnel, because bluntly tunneling beneath the mucosa is frequently impossible in these bladders.

children is now feasible,[7,21] and he may need this in the future as he grows older and develops more body mass. One patient in this series has already undergone renal transplantation for which he was originally referred. (A reconstructive procedure was performed in the face of severely depressed renal function in order to refunctionalize the bladder, and gain another year of time before resorting to transplantation). There are ten other children in this series whose renal function is sufficiently low that eventual transplantation may be necessary. Meanwhile they are enjoying a satisfactory quality of life with a closed urinary tract, without a bag, and we believe they represent better candidates for transplantation with a functioning bladder than with a urinary diversion.

Case 3. (Fig. 8) This patient was referred at age 2 years in 1967 with an obstructed ileal loop for revision. During infancy urinary infection had occurred; cystogram showed massive reflux (Fig. 8a). An end ureterostomy was performed, following which the patient did poorly; later high pyeloileal conduit was performed. When this became obstructed, the patient was referred for revision. A new ileal conduit was fashioned at that time, April 1967. The patient did well clinically during the next six years, although continuous antimicrobial therapy was required to maintain a sterile urine. Although loopogram (Fig. 8b, c) showed considerable hydronephrosis BUN was 9 mg. % and creatinine 1.5 mg. %. The cystogram showed a small bladder, with apparently normal sensation, but the patient was not able to empty it. Undiversion was performed in June of 1973 (Fig. 8d). Urethral valves were destroyed endoscopically. The conduit was redundant between the two renal pelves, and so the right renal pelvis was advanced to a more proximal point along the conduit (Fig. 8c), which provided enough conduit distally to reach the bladder. The conduit was tapered from the right renal pelvis downward and reimplanted into the bladder (Fig. 8d). Cystogram two weeks post operatively showed dye entering only the lower two inches of the tapered conduit. (A subsequent cystogram has not been performed yet). Left antegrade percutaneous pyelography showed delay in passage of dye from the left renal pelvis into the loop, owing to redundancy, which was evident also in review of previous films. Therefore, five weeks after the

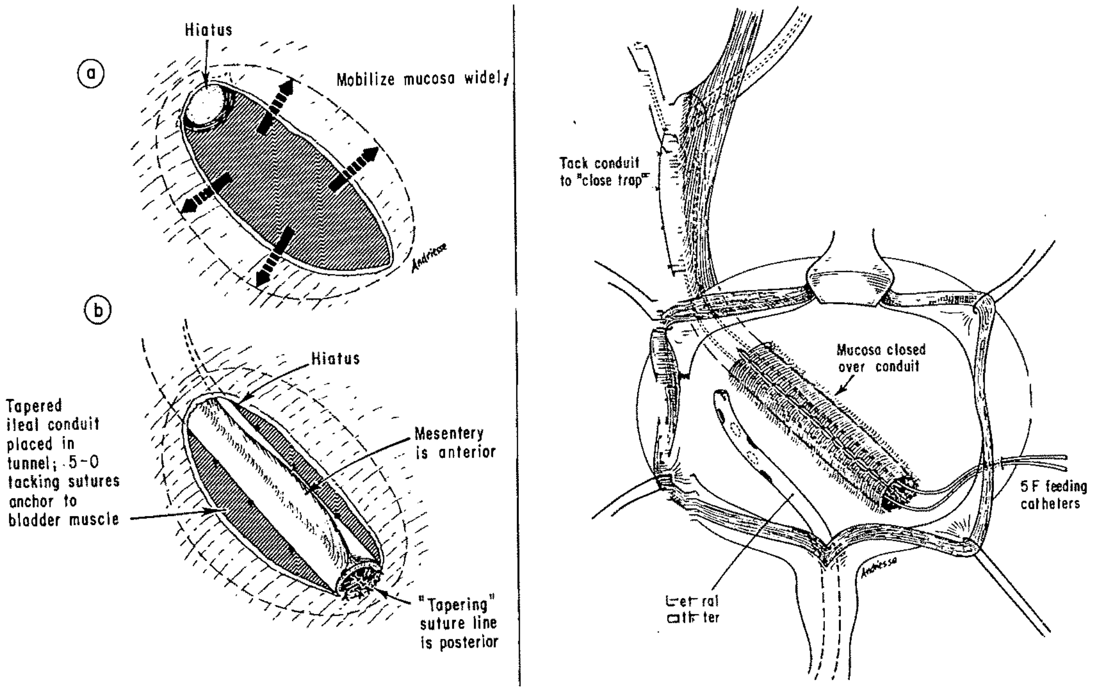

Hiatus
(a)
Mobilize mucosa widely
Andriesse
(b)
Hiatus
Tapered ileal conduit placed in tunnel; 5-0 tacking sutures anchor to bladder muscle
Mesentery is anterior
"Tapering" suture line is posterior
Tack conduit to "close trap"
Mucosa closed over conduit
5 F feeding catheters
Ureteral catheter
Andriesse

FIG. 5g. (Left) Mucosa is mobilized widely, conduit is placed in it, with the tapering suture line posteriorly. Excess fat is trimmed from the mesentery, which lies anteriorly, and excess length of conduit discarded. FIG. 5h. (Right) Soft drainage catheters are passed up the ureters for temporary decompression for 10–12 days.

lower operation, the left renal pelvis was tapered, shortened, and reanastomosed to the loop; the upper section of the conduit was not tapered since it did not appear very dilated (Fig. 8d). An intravenous pyelogram six months later (Fig. 8e) showed satisfactory function bilaterally, and a normal sized bladder. The patient is well (Fig. 8f), has normal urinary control, is free of urinary infection, and has undergone tremendous psychological improvement having disposed of his urinary appliance. Renal function remains stable.

Comment

Like case 2, this patient was doing well with a long standing high pyeloileal conduit, although with a definite limitation in lifestyle and with continuing low grade bacilluria. Redirecting the flow of urine to his bladder did not cause any impairment in his renal function. Having his urinary tract closed to outside contamination has resulted in a consistently sterile urine which he has never had previously.

Case 4. (Fig. 9) This 11-year-old boy was referred for undiversion in January, 1974. In August, 1963 at age three months urinary infection occurred; cystography (Fig. 9a) showed massive reflux and hydronephrosis. Subrapubic cystostomy was performed. At age two years, September 1965, cystogram through the suprapubic tube (Fig. 9b) showed continuing reflux. The

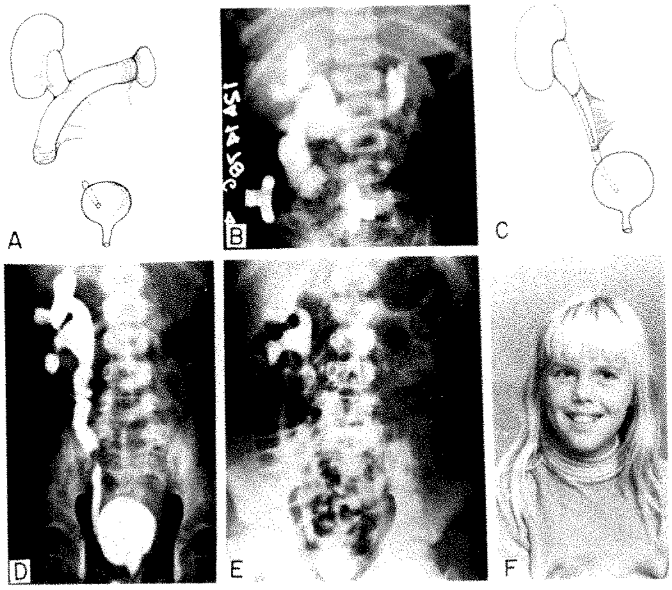


FIG. 6. Case 1: (A) Anatomy before reconstruction. (B) Retrograde filling of ileal conduit at age 6 years. (C) Operative reconstruction at age 6 years. (D) Antegrade study through temporary nephrostomy 2 weeks postoperatively. (E) Intravenous pyelogram 5 years postoperatively. (F) The patient at age 11 years.

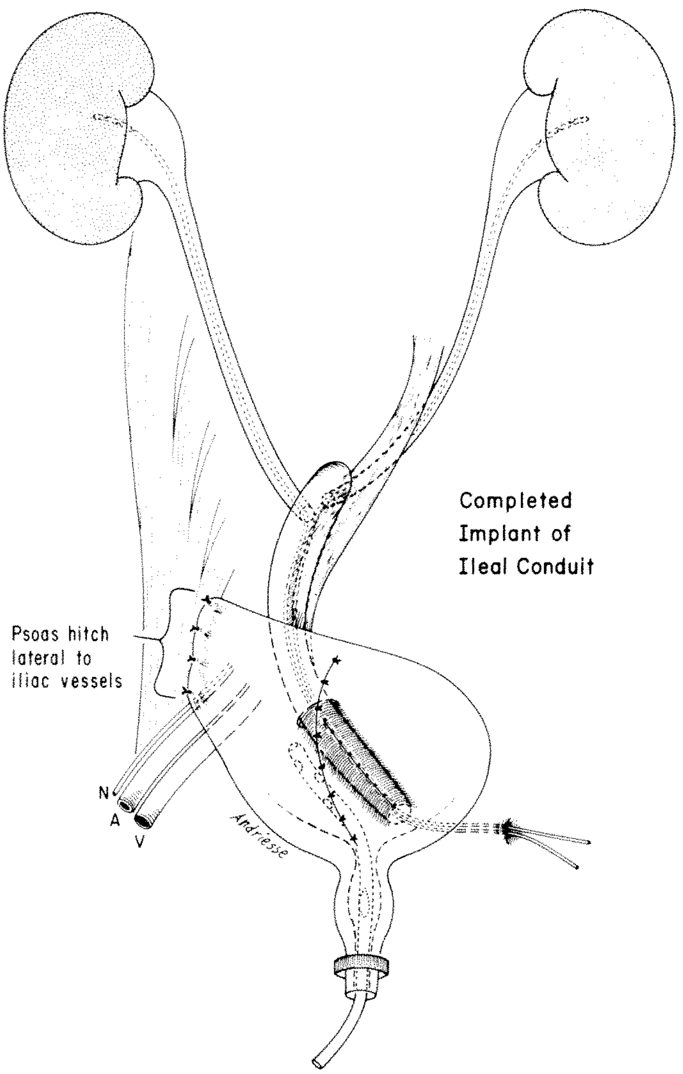


FIG. 5i. Completed implant with anchoring of bladder lateral to point of entry of conduit to immobilize it, which will protect against angulation when the bladder fills. This helps achieve adequate tunnel length of 3 to 5 cm. in very small contracted bladders.

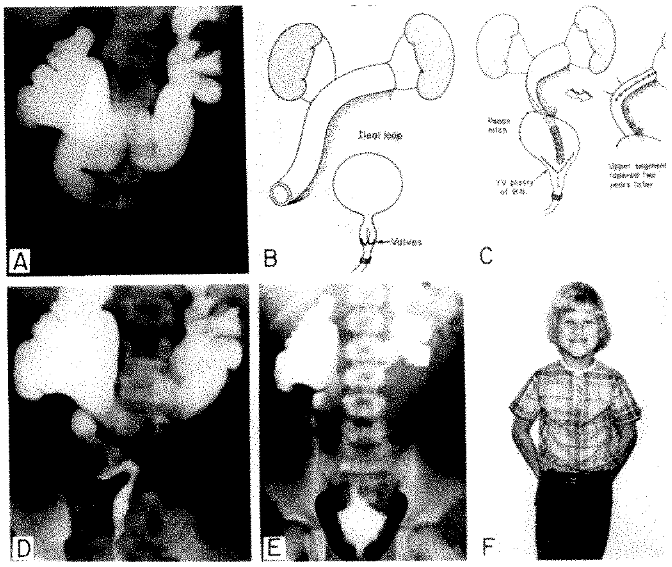


FIG. 7. Case 2: (A) Retrograde filling of pyelo-ileal loop preoperatively. (B) Preoperative anatomy. (C) Operative reconstruction, in stages. (D) Retrograde study two months after tapering and reimplanting lower conduit. (E) Percutaneous antegrade study after tapering upper conduit. (F) Patient at age 10 years.

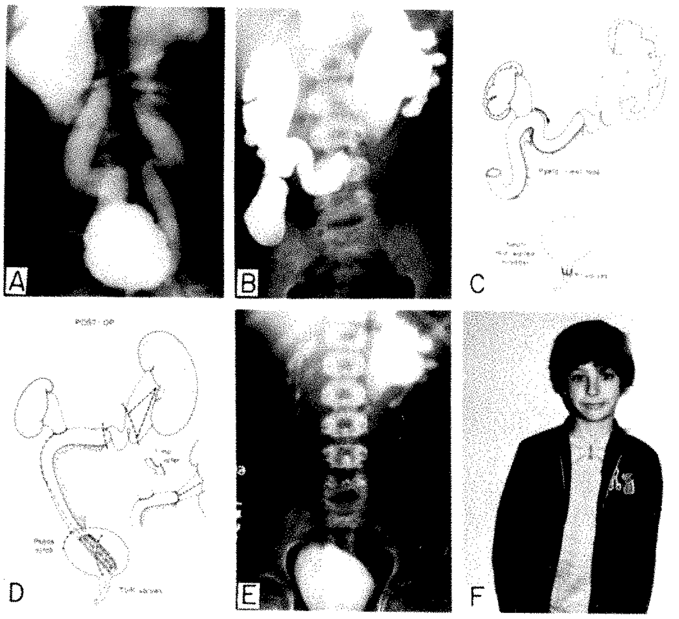


FIG. 8. Case 3: (A) Cystogram during infancy showing massive reflux. (B) Retrograde filling of ileal loop before undiversion. (C) Anatomy before undiversion. (D) Operative reconstruction, in stages, at age 8 years. (E) I.V.P. 6 months after reconstruction. (F) Patient at age 8 years.

patient had formed bilateral renal calculi; bilateral nephrolithotomy was performed. In March, 1966 an ileal conduit was performed. Following this, his clinical course was much improved, although at age 3½ a second left nephrolithotomy was required. He was maintained on low dose suppressive antimicrobial therapy initially, but during the three years before referral, the urine had been consistently sterile off medication. Simultaneous cystogram and loopogram (Figs. 9c, d) showed a small bladder, and a satisfactory ileal conduit. The patient could not empty the bladder, but seemed to have normal sensation. At operation (Fig. 9e) valves were resected endoscopically, the loop was tapered and reimplanted with a long submucosal tunnel. I.V.P. two weeks postoperatively (Fig. 9f) was satisfactory. Cystography did not show reflux. The patient had frequent urination initially, but at four weeks postoperatively had developed normal urinary frequency and control, with a bladder capacity of about 350 cc.

Comment

This case is anatomically similar to the majority of youngsters who have undergone urinary diversion who might be considered for operation. In 6 of the 10 cases with ileal conduits in this series the reconstruction was performed in this manner.

Case 5. (Fig. 10) This 13-year-old boy was referred in May of 1973 for undiversion. At age 4 months an inguinal hernia operation was followed by urinary extravasation and reoperation, but no investigation of the urinary tract was carried out. At age one year investigation was performed because he ran a constant low grade temperature and was anemic. Hydronephrosis was discovered and was considered secondary to an atonic bladder. Suprapubic cystotomy was performed, but the patient had continuing urinary infection, and an ileal conduit was constructed in 1962 at age two years. Aside from revision of the stoma in 1966, he was clinically well. There was no clinical evidence of urinary infection, although cultures were followed infrequently; he was on no medication. Preoperative investigation (Figs. 10a, b) showed a very low ileal conduit, and a bladder with apparently normal sensation, which would hold a maximum of 40 cc of

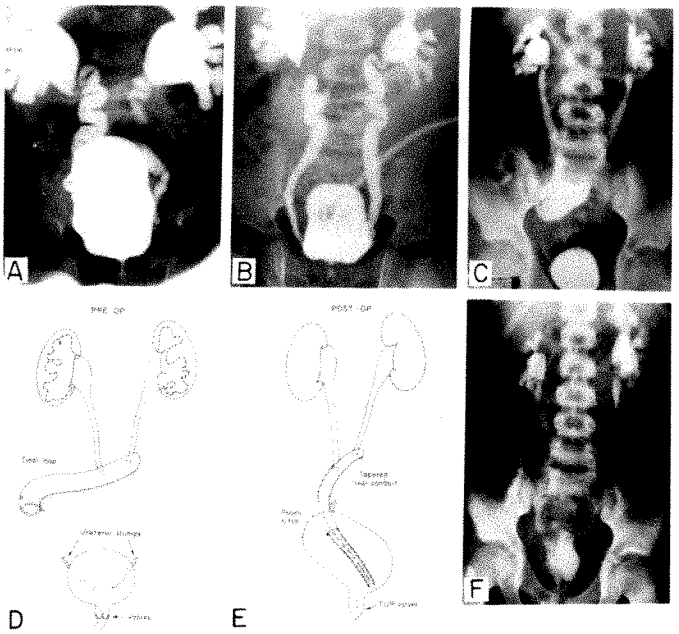


FIG. 9. Case 4: (A) Cystogram age 3 months with massive reflux. (B) Cystogram age 2 years through suprapubic tube. (C) Simultaneous loopogram and cystogram prior to undiversion at age 11 years. (D) Anatomy preoperatively. (E) Postoperative anatomy. (F) I.V.P. two weeks postoperatively.

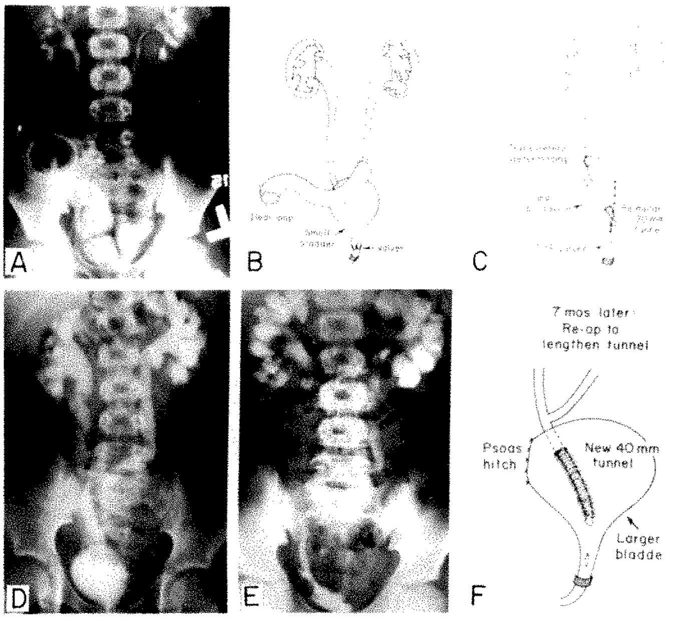


FIG. 10. Case 5: (A) Preoperative I.V.P. (B) Preoperative anatomy. (C) Operative reconstruction. (D) I.V.P. two weeks after reconstruction. (E) Cystogram 6 months later with reflux. (F) Reoperation to correct reflux.

water. In May 1973, operation was performed (Fig. 10c) endoscopically resecting urethral valves, reimplanting the right ureter into the bladder, and a left to right transureteroureterostomy. At operation, with a Foley catheter in the bladder, an attempt was made to dilate the bladder hydrostatically; it was a tiny structure, only the size of a squash ball. I.V.P. two weeks postoperatively (Fig. 10d) showed satisfactory function, moderate hydronephrosis, and still a small bladder. Gradually during the next three months the patient developed a normal capacity bladder and satisfactory urinary control. Cystogram six months later (Fig. 10e) in November, 1973, showed considerable vesicoureteral reflux. Although he was clinically well, this was considered unacceptable and reoperation was performed January, 1974, 8 months after his "undiversion" (Fig. 10f). The bladder size was now considerably larger. The reimplanted ureter was mobilized and reimplanted once again, obtaining a tunnel of about twice the length of the initial one. A psoas hitch was done to immobilize the bladder wall at the point of entry of the ureter and to obtain additional tunnel length. Cystogram two weeks later showed no reflux. Followup I.V.P. showed considerable improvement. He is free of urinary infection, on no therapy, and is leading a normal life for an adolescent boy.

Comment

What it means to a youngster to get rid of an external urinary appliance, when that is possible, may best be underscored by the written words from his mother, who is an operating room nurse:

> Since reconstructive surgery in 1973 his mental attitude and morale have improved 100%. His social relationships with friends, both at home and school (especially in gym class) have improved and broadened. He is now anxious to bring friends home to stay overnight and to stay at the home of friends. His school grades went up from average to honor roll standing, and he no longer avoids showering with the boys in gym class. To us, the biggest surprise which showed the depth of his feelings, was when he said, "Gee, now I can get married!"

Undiversion Following Prior Loop Ureterostomy

This method of urinary diversion has been used widely by many surgeons in recent years as a means of providing drainage of the kidney by a relatively simple means and without the use of an inlying tube, which is invariably accompanied by infection. Ten of the cases in this series were undiversions from prior loop ureterostomy, which had been done as a temporary measure in seven children and as a permanent diversion in three. In our own case material of infants with severe obstructive uropathy we have preferred a direct reconstructive approach rather than resorting to a preliminary exteriorization procedure such as loop ureterostomy, although certainly there is more than one way to accomplish the desired end of repairing the urinary tract. From our experience with reconstructing children with previous ureterostomy, however, I believe that a ureterostomy does *not* make easier the subsequent reconstruction, and that it can, in fact, complicate reconstruction. It does, on the other hand, permit deferring an ultimate reconstruction until the child is older which may be desirable if the youngster is initially very ill or if the surgeon has not much experience in undertaking major surgery in small infants. A severely contracted bladder may be the price of such delay, however.[18,29] In our opinion there is no easy way to manage these cases. They are extremely difficult whether repaired primarily or after a prior diversion.

Case Reports

Case 6. (Fig. 11) This patient was referred at age 3½ years, in January, 1973, for urinary reconstruction. At six weeks of age he was investigated because of failure to thrive, was found to have a distended bladder and azotemia. Intravenous pyelogram (Fig. 11a) showed severe hydronephrosis with markedly reduced function. Cystogram (Fig. 11b) showed typical findings of severe type I urethral valves. The prostatic urethra was dilated and elongated and the bladder neck was massively hypertrophied; there was a paraureteral diverticulum on the right side. Loop ureterostomy was performed, following which his condition improved. There was no evidence of urinary infection during the ensuing years while urine drained from the flanks bilaterally.

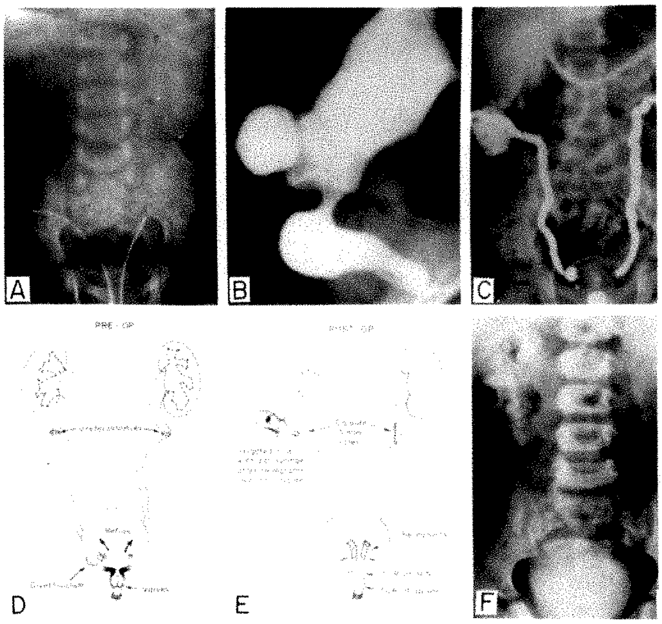


FIG. 11. Case 6: (A) I.V.P. at age 6 weeks showing severe bilateral hydronephrosis and diminished function. (B) Cystogram showing Type I valves obstructing urethra, with dilated prostatic urethra, hypertrophied bladder neck, and right paraureteral diverticulum. (C) Antegrade filling of ureters through distal limb of ureterostomies at age 3½ years. (D) Preoperative anatomy. (E) Operative correction in stages, first the lower tract, and closure of ureterostomies 3 months later. Frequent irrigation of distal limb of ureterostomies while waiting closure. (F) I.V.P. two months postoperatively.

The ureterogram at age 3½ years (Figs. 11c, d) showed slightly dilated ureters, a paraureteral diverticulum on the right, typical urethral valves, a small bladder, and vesicoureteral reflux. Operation consisted of endoscopic resection of valves, bilateral ureteral reimplantation, and repair of the diverticulum. Starting ten days following the ureteral reimplantation surgery, the parents were instructed in t.i.d. irrigations of both distal ureters with a rubber ear syringe (Fig. 11e). Two months later the patient was readmitted and bilateral ureterostomy closure was performed. At this same occasion the bladder neck was endoscopically incised at 6 o'clock and 12 o'clock to open it further, since it showed great residual hypertrophy. I.V.P. two months postoperatively (Fig. 11f) showed satisfactory visualization of both upper tracts which were moderately dilated. This patient is currently well, BUN 25 mg%, creatinine 1.2 mg%, but with reduced creatinine clearance, as expected, measuring 14 L absolute. The urine is sterile.

Comment

This is the type of temporary diversion which has been practiced most widely in recent years by many surgeons when confronted with a young infant with uremia. It does permit deferring a definitive reconstruction until the child is larger, yet we believe that most of these babies can be treated by a direct reconstructive procedure provided the surgeon is very experienced in operating on the very young infant. Preliminary ureterostomy does obviate need for operating on a sick infant, but requires a second procedure to close each ureterostomy, which is itself not always an easy operation.

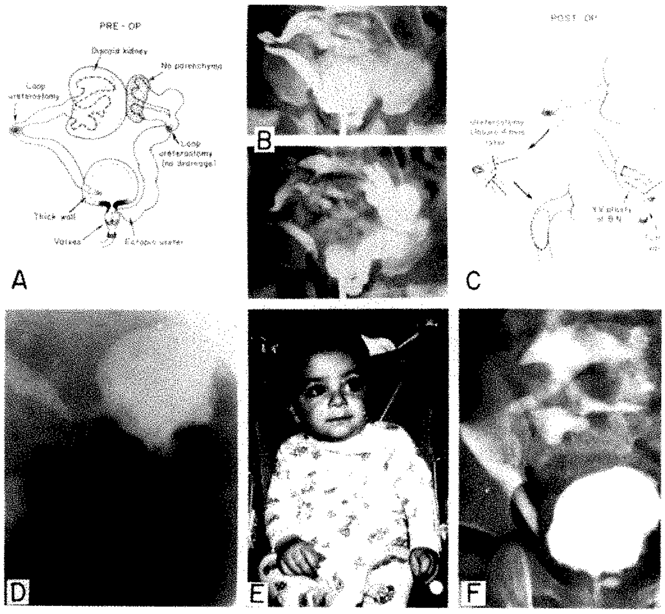


Fig. 12. Case 7: (A) Preoperative anatomy, age 5 months. (B) Preoperative x-rays showing bilateral flank ureterostomy, and ectopic left ureter entering prostatic urethra. (C) Staged operative correction, first the lower tract and closure of ureterostomy 4 months later. (D) Antegrade filling of ureter through ureterostomy before its closure, demonstrating satisfactory drainage into bladder, and long ureteral vesical tunnel. (E) The patient at age 9 months. (F) I.V.P. 7 months after closure of ureterostomy, and 11 months after lower tract reconstruction.

Further it can complicate the lower reconstruction if the ureter is tethered upward by ureterostomy, or if the blood supply of the ureter is jeopardized (cases 8, 9, 12). We believe it is very important to irrigate the distal limb of a loop ureterostomy after reimplanting the lower ureters until the ureterostomies are closed, for we have observed in 3 children complete healing over of the ureteral orifice in a "dry reimplant," through which no urine was passing. In addition we think that irrigation may provide physiotherapy for the long defunctioned bladder by stretching it periodically from above in preparation for closure of ureterostomy several weeks later.

Case 7. (Fig. 12) This baby was referred at age 5 months for urinary reconstruction. At three months of age he had presented with uremia, acidosis, and urinary infection, and was treated by immediate bilateral loop ureterostomy. The left stoma drained nil but the right drained well. His condition improved, and on admission the BUN was 24 mg% and creatinine 1.4 mg%. Investigation showed very unusual anatomy (Figs. 12a, b), including urethral valves, the left ureter entering ectopically into the prostatic urethra, nonfunction of the left kidney, and a disc-shaped, ectopic right kidney in the lower mid-abdomen. Operative reconstruction (Fig. 12c) included endoscopic resection of valves, removal of the ectopic left ureter and its dysplastic kidney, with reimplantation of the right ureter. If there had been insufficient length of the right ureter to achieve a satisfactory reimplantation without tension, the ureterostomy would have been mobilized and moved to a lower position. The ureter was reimplanted diagonally across the trigone to achieve satisfactory tunnel length in this contracted bladder. A Y-V plasty was performed to the anterior bladder neck. The parents were instructed in irrigation of the distal ureterostomy stoma to keep open the ureteral reimplant and to stretch up the bladder. He was admitted four months later for closure of the ureterostomy (Fig. 12c). Preliminary ureterogram (Fig. 12d) showed satisfactory passage of dye instilled above through the lower ureter into the bladder with no persisting valve obstruction of the urethra. Cystography showed no reflux. The infant (Fig. 12e) has done well following this reconstructive procedure. I.V.P. 7 months later (Fig. 12f) shows satisfactory function of his peculiar kidney.

Comment

Although we have not resorted to loop ureterostomy in our own cases, we believe it was the procedure of choice in this particular infant with very unusual anatomy. It provided immediate relief of uremia and the useful information that there was no functioning parenchyma on the left side. If one had pursued a direct reconstructive approach there might well have been a bilateral reconstruction, and discovery after the fact that there was no function on the left. One should be suspicious, however, that there is no functioning parenchyma in any case of an ectopic ureter entering the prostatic urethra of a male baby. When ureterostomy is elected we believe that definitive reconstructive surgery should be performed in the near future, as it was in this case, instead of waiting for several years as is commonly elected.

Case 8. (Fig. 13) This lad was referred in July 1973, at age 2½ years for a secondary reconstruction procedure. As an infant at age two months he had become extremely ill, and urinary investigation disclosed severe bilateral hydronephrosis, with extravasation of dye around the right kidney (Fig. 13a). Bilateral loop ureterostomy was performed and he did well. In September 1972, at age 22 months, bilateral ureteral reimplantation was performed, but the surgeon was not satisfied with the result because the ureters were tethered superiorly so that there was insufficient length of the lower ureters to achieve suitable reimplantations. Subsequent cystogram showed free bilateral reflux. Investigation on admission (Fig. 13b, c) showed a straight course of ureters from the ureterostomy sites to the bladder, with ureters implanted in the dome of the bladder, and some residual valves. Operative reconstruction was performed (Fig. 13d), through wide transabdominal exposure. Mobilization of the lower ureters disclosed that they were too short to reimplant without tension, except by mobilizing the ureterostomies. This was done, therefore, with great care to their blood supply. Although the procedure was long and tedious, the patient did well. A retrograde pyelogram (Fig. 13e) six months later showed satisfactory contour of ureters. There was no reflux on cystogram. I.V.P. in March of 1974 (Fig. 13f) showed moderate upper tract dilatation, but satisfactory function. The bladder capacity is now normal, although it held only 15cc preoperatively. The youngster's BUN is 16 mg%, creatinine 0.5 mg% and creatinine clearance 45 L absolute.

Comment

A previously operated case like this represents one of the most difficult technical undertakings in surgery of infants and children in our opinion. There was no alternative but to mobilize the ureterostomies in order to gain sufficient length to perform satisfactory ureteral reimplantations, yet realizing that this could be hazardous to ureteral blood supply. (All mobilization of the ureters was carried out in the lateral gutters away from their attachment to the peritoneum medially where the blood supply is located). Alternatives which were considered included relocating the ureterostomies at a lower position, but not closing them, at the time of reoperating the lower ureters; and performing a preliminary closure of both ureterostomies as a separate step before operating on the lower ureters. However, because blood supply did not seem unduly precarious, we elected a total reconstruction in one stage for this youngster. As in most of these undiversion cases, the exposure of choice is a long midline incision from xyphoid to pubis to gain easy access to all levels of the urinary tract. When the child has flank ureterostomies, it is our practice to do a total body prep and drape below the mid thorax, to permit working in front, or rolling the child for access to the flank. These operations frequently last 6–8 hours. They require expert pediatric anesthesia and after care as well as meticulous intraoperative management. *There is no margin for technical misadventure.*

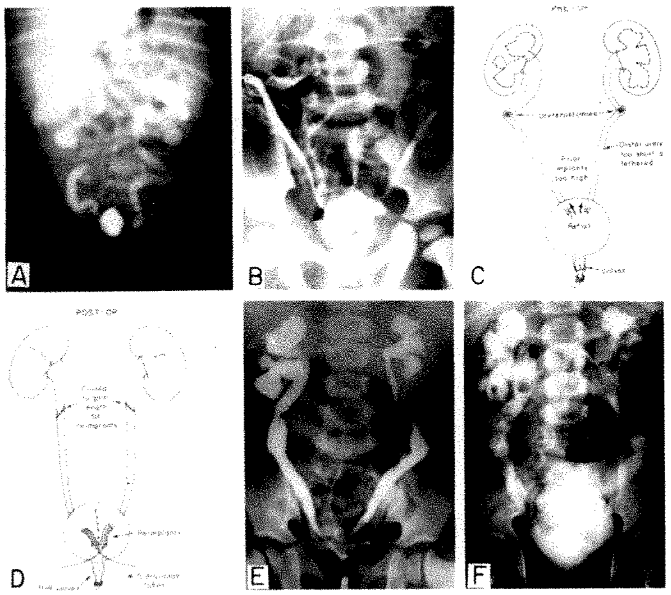


FIG. 13. Case 8: (A) I.V.P. at age 2 months. Note perirenal extravasation on right side. (B) Ureterograms on admission, with straight course of ureters from flank to bladder, because they were tethered upward by the ureterostomies. (C) Preoperative anatomy. (D) One stage operative correction. (E) Retrograde pyelogram 6 months later. (F) I.V.P. 9 months postoperatively.

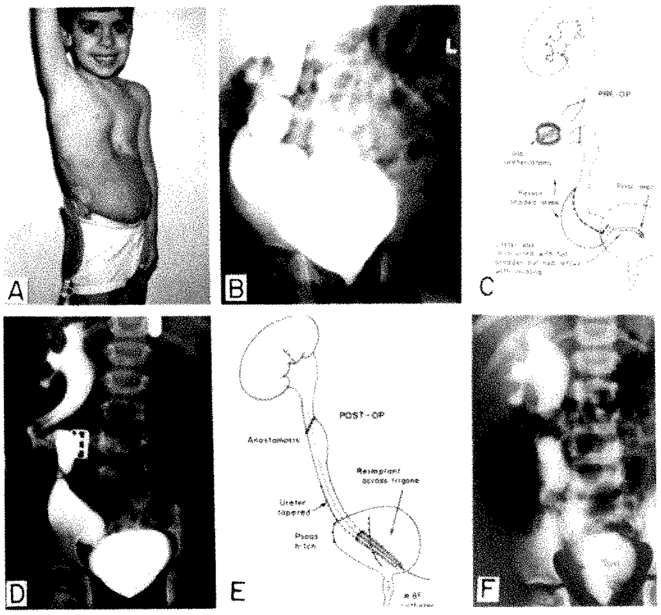


FIG. 14. Case 9: (A) Patient preoperatively, age 5 years. (B) Cystogram at age 2½ years, after left nephrectomy and right ureteral reimplantation, but before right ureterostomy. Massive reflux. (C) Preoperative anatomy and plan of reconstruction, with careful preservation of blood supply to ureter. (D) X-ray study of urinary tract by injecting both limbs of ureterostomy preoperatively. (E) Anatomic reconstruction. (F) I.V.P. 2 weeks postoperatively.

Case 9. (Fig. 14) This five-year-old patient was referred in March 1974 for reconstructive surgery. He had the "Prune Belly Syndrome" (Fig. 14a) with protuberant abdomen, pectus excavatum, and a urinary appliance on his side draining a flank ureterostomy. At three months of age he had urinary infection and was found to have severe bilateral hydronephrosis with vesicoureteric reflux and hypoplasia of the left kidney. Right ureteral reimplantation was performed, and at age five months left nephrectomy. Because of poor social circumstances followup was not possible by the first surgeon. At age 2½ years he was seen at another institution for urinary infection. Cystogram (Fig. 14b) showed massive reflux. Loop ureterostomy was performed and the patient thrived thereafter. When referred at age 5 years (Figs. 14c, d) investigation showed a satisfactory kidney, loop ureterostomy, bulbous dilatation of the lower ureter, and a small terminal ureter. It appeared obstructed when the bladder was filled, but showed reflux during micturition. An extensive operative reconstruction was performed (Fig. 14e). With the patient circumferentially prepped and draped, to afford access anteriorly or posteriorly at the ureterostomy site, exploration was carried out through a long midline transabdominal exposure. The ureter was dissected from the bladder intravesically and extravesically, with great care to preserve its blood supply medially and its attachment to the peritoneum. The terminal ureter which had been previously tapered was unsatisfactory (Fig. 14c). It was necessary to gain additional length for a new tapering and reimplantation procedure. This required taking down the ureterostomy, carefully guarding its blood supply. It was elected not to place a nephrostomy tube in this kidney with nondilated calices and infundibula, not wishing to obstruct any part of the kidney drainage by such a tube. Instead, upper tract decompression was maintained for 12 days from below using a #8 French feeding catheter through the side wall of the bladder up to the kidney. The patient had an uneventful convalescence. I.V.P. two weeks postoperatively showed satisfactory function (Fig. 14f). Cystogram showed satisfactory emptying with no reflux.

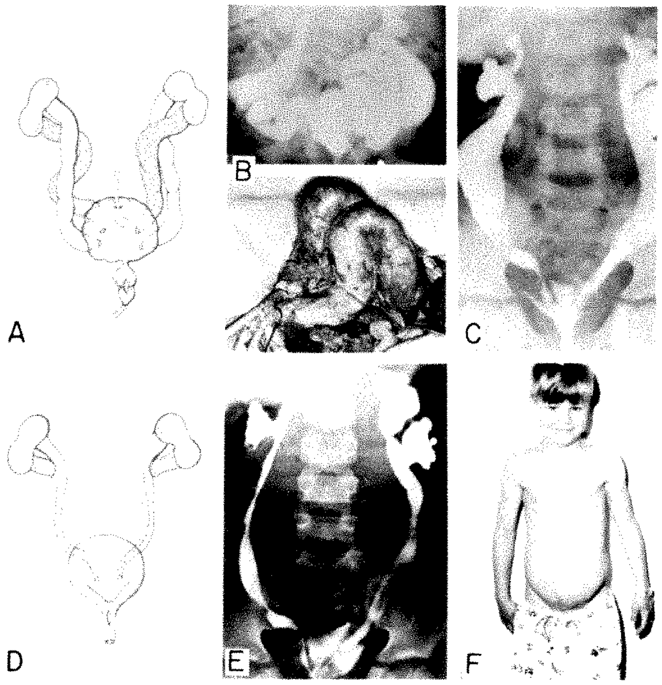


FIG. 15. Case 10: (A) Preoperative anatomy. (B) (Top) Cystogram age 3 months showing dilated, tortuous ureters. (Bottom) Two left megaureters at operation. (C) Retrograde pyelogram 6 months after initial operative procedure. All four ureters were straightened, the lower part of the upper pole ureter was tapered on each side, and reimplanted. The adjacent lower pole ureter was anastomosed end to side into the upper pole ureter just above the bladder. (D) Final reconstruction two years later, removing the remaining lower pole ureters, with bilateral pyeloureterostomy and tapering of the rest of each upper pole ureter. (E) Retrograde pyelogram at age 9 years. (F) The patient at age 9 years.

Comment

It had been previously considered impossible to reconstruct this child after an initial failure and subsequent ureterostomy. Persistence is imperative in dealing with these difficult cases. In our own experience with megaureter there is presently a complication rate of about 8%, i.e. requiring reoperation for obstruction or persisting reflux. We have not hesitated, therefore, to operate a second time, and occasionally a third time until a satisfactory anatomic solution is achieved. This, we feel, is preferred to taking a defeatist attitude and electing permanent urinary diversion prematurely. Reoperation should be deferred for several months in case of technical failure to allow subsidence of post operative inflammatory changes.

Undiversion After Cystostomy

In three cases a suprapubic tube had been placed in children with a presumably short term life prognosis. Although this type of drainage can be satisfactory in some patients, in many it does not adequately decompress the upper tracts, and it poses the problem of continuing bacilluria secondary to an inlying foreign body.

Case Reports

Case 10. (Fig. 15) This boy was referred at age six years for possible reconstructive surgery. At birth it had been noted that he had the "Prune Belly Syndrome." At age 3 months when urinary infection occurred, a suprapubic tube was placed. He was maintained on chloromycetin continuously for five years to suppress infection! In Fig. 15a is shown diagramatically his anatomy with bilateral double megaureters. Figure 15b (top) shows cystogram as an infant, outlining megaureters, and Fig. 15b (bottom) shows the two left megaureters exposed at operation. Endoscopically there were thick valve-like folds arising lateral to the veru; they were incised. The bladder was thick walled and vascular. The previous cystostomy site was excised. The two ureters on each side were straightened, shortened, and tapered, reimplanting one and anastomosing the other to it just above the bladder. Retrograde study six months later is shown in Fig. 15c. Two years later further surgery was done on each side, through flank incisions, removing the extra length of lower pole ureter, performing lower pole pyeloureterostomy, and tapering the upper segment of the remaining upper pole ureter (Fig. 15d). Retrograde pyelogram at age 9 years, in 1973, is shown in Fig. 15e.

Comment

This youngster's parents were told when he was an infant that he had only a few months to live. This underscores the fact that children with hydronephrosis will often do much better than one might guess initially. Cases with the "Prune Belly Syndrome," which is poorly understood, are perhaps among the most difficult in planning reconstruction. The ureters are generally extremely tortuous and elongated, and the bladder is often thick walled and vascular, making ureteral reimplantation difficult. Nonetheless we believe that many of them can be improved by reducing the enormous reservoir capacity of dilated tortuous ureters, abolishing reflux, and improving bladder emptying. In many of the children with "Prune Belly Syndrome" there are also dysplastic kidneys.

Undiversion From End Ureterostomy

Five patients of our 32 had undergone exteriorization to the skin of the lower end of the ureter as a permanent method of diversion. In three of the five low grade continuing bacilluria accompanied this method of diversion.

Case Report

Case 11. (Fig. 16) This youngster was referred in January 1973 at age 12 years for possible reconstruction. At age 9 months he had urinary infection, found to be secondary to ureterocele with bilateral massive hydronephrosis (Fig. 16a). Initial surgery consisted of incision of the ureterocele, with suprapubic cystostomy; later there was a Y-V revision of the bladder neck at age 2 years. At age 3 years bilateral, end-cutaneous ureterostomies were performed. Study on admission (Fig. 16b, c) showed a small bladder, with residual ureteral stumps bilaterally, duplex collecting systems, good renal parenchyma remaining in only the upper pole of the left kidney. There was no drainage from the ureterostomy stomas on the right side.

Operation (Fig. 16d) included right nephroureterectomy, removal of the lower pole ureter on the left with preservation of the blood supply of the adjacent upper pole ureter, lower pole pyeloureterostomy, repair of the ureterocele defect in the trigone, excision of three ureteral stumps, and ureteral reimplantation. The procedure was done with long transabdominal exposure and lasted for 9 hours. The patient has done well post operatively, with consistently sterile urine. Intravenous pyelogram 14 months later was satisfactory (Fig. 16e). His serum creatinine is 0.7 mg%, BUN 16 mg%. The average value of 2 postoperative creatinine clearances is 74 L absolute, reflecting hypertrophy of the left upper pole in response to loss of the right kidney function as an infant. The patient is leading a normal active boyhood (Fig. 16f).

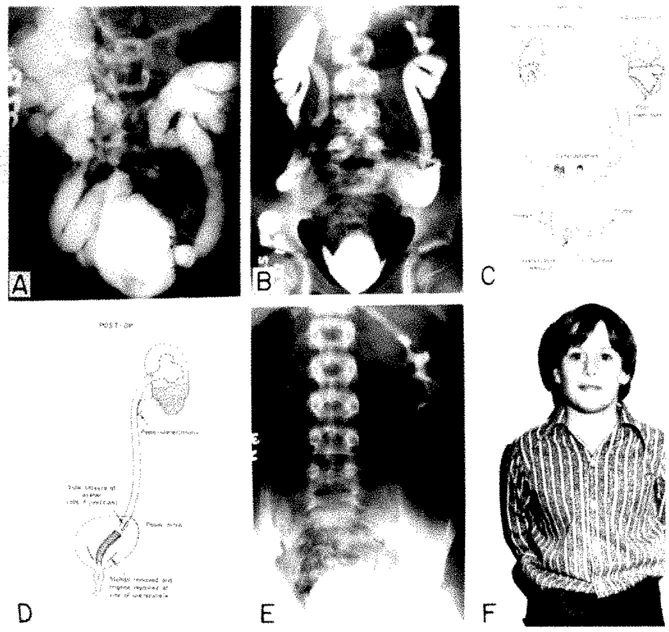


Fig. 16. Case 11. (A) Cystogram age 9 months with bilateral massive hydronephrosis caused by ureterocele. (B) Preoperative cystogram and ureterograms before reconstruction, showing small bladder, residual ureteral stumps and tortuous ureters bilaterally. (C) Diagram of preoperative anatomy. (D) Operative correction. (E) I.V.P. 14 months postoperatively. (F) The patient at age 13 years.

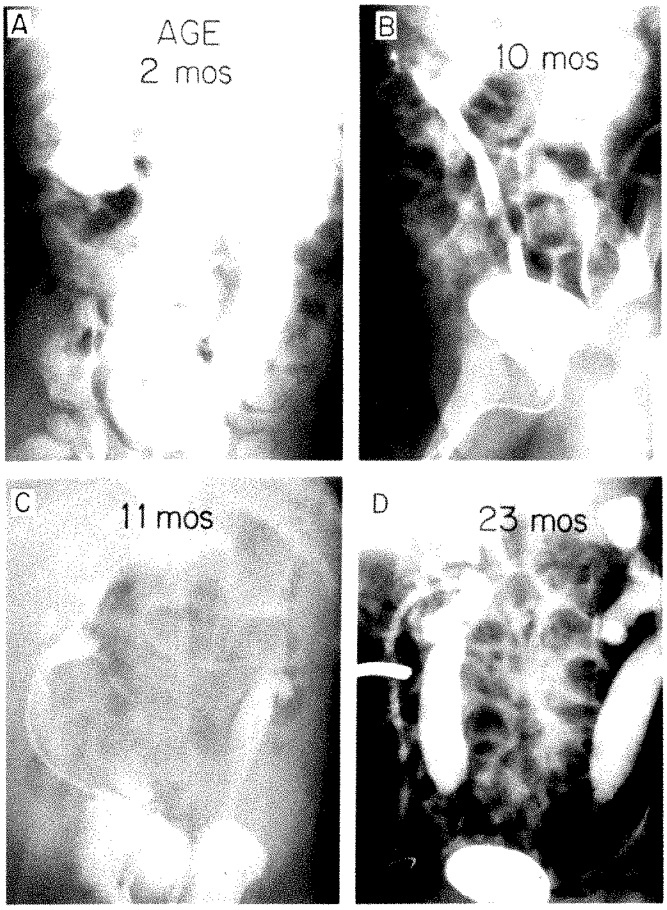


Fig. 17a. Case 12: (A) I.V.P. at age 2 months showing bilateral severe hydronephrosis. (B) Ureterograms at age 10 months, after loop ureterostomies. (C) Age 11 months, after closure of ureterostomies, and subsequent lower ureteral tapering and reimplantations. There is bilateral paravesical extravasation of dye from necrosis of both lower ureters. Bilateral nephrostomy was performed. (D) Cystogram and nephrostogram at 23 months, before reconstruction, showing no continuity between ureters and bladder.

Comment

Refunctionalization of this youngster's urinary tract, has resulted in sterilization of his urine and improvement in his lifestyle. Cystogram one year following reconstruction showed some vesicoureteral reflux. It is planned to watch this at present. If reflux persists we will likely reoperate to correct it, which can be done with success in most instances.[11]

Undiversion From Nephrostomy

There were 3 children with nephrostomies referred for possible reconstruction and a fourth with both nephrostomy and cystostomy of 16 years duration.

Case Reports

Case 12. (Fig. 17) The patient was referred in June 1973 at age 23 months for possible reconstruction. At age two months urinary infection had occurred and he was found to have severe bilateral hydronephrosis (Fig. 17a). Bilateral loop ureterostomy was performed and subsequent study showed diminished size of the dilated ureters (Fig. 17b). The ureterostomies were closed and shortly thereafter bilateral lower ureteral tapering and reimplantation was performed; there was necrosis of both lower ureters with extravasation (Fig. 17c). Bilateral nephrostomy was performed. Investigation on referral (Figs. 17d, e) showed that there was no continuity between the dilated ureters and the bladder. Operation was performed through a long transabdominal exposure with circumferential prep and drape to afford access to the flanks. It was possible to secure adequate length of the left ureter to reach the bladder by taking down the nephrostomy, pexing the kidney downward, and mobilizing the ureter with careful preservation of its blood supply medially. A kink at the previous ureterostomy site on the left was straightened by a Heineke-Mikulicz-plasty. The right ureter was too short to reach the bladder, and, further, the bladder was too small to accommodate two ureteral reimplantations, and so transureteroureterostomy was performed. The bladder was tacked upward to help immobilize the reimplant. Percutaneous antegrade pyelogram (Fig. 17g) showed satisfactory drainage into the bladder. Subsequent cystograms have shown no reflux. The child (Fig. 17h) has done well clinically in the 11 months since reconstruction.

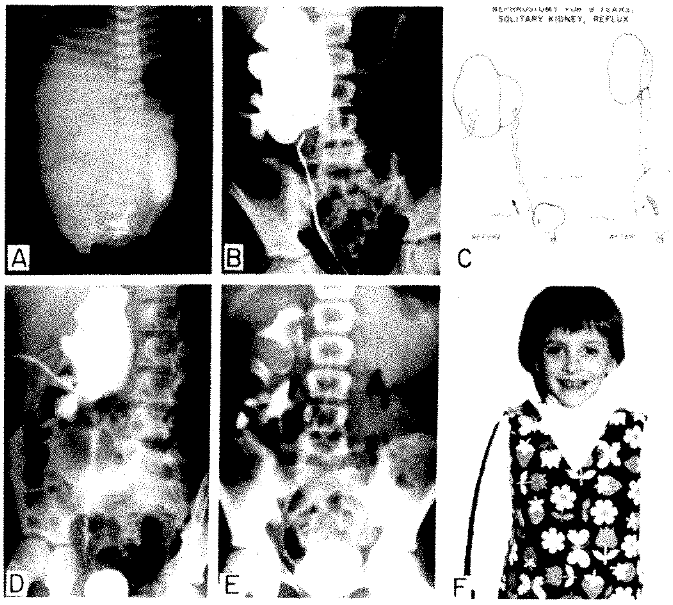


Fig. 18. Case 13: (A) I.V.P. age 5 weeks, showing solitary right kidney with enormous hydronephrosis. (B) Simultaneous nephrogram, retrograde ureterogram before reconstruction age 9½ years. (C) Operative reconstruction in stages, first a dismembering pyeloplasty, and 7 months later ureteral reimplantation to correct reflux. (D) Nephrostogram 2 weeks after upper tract repair. (E) I.V.P. 6 months after upper tract repair. (F) Patient at age 10 years.

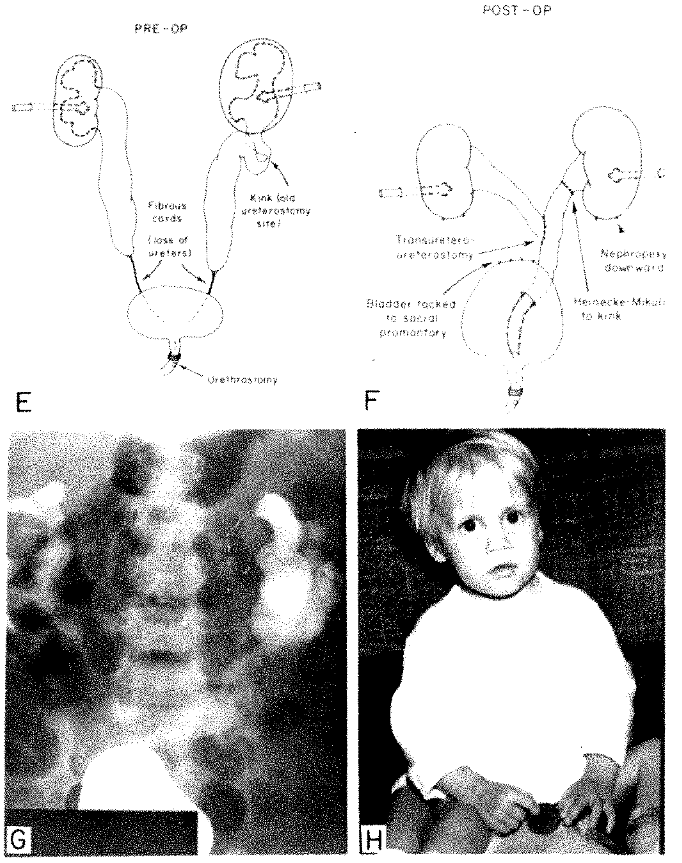

PRE-OP
POST-OP
Fibrous cords (loss of ureters)
Kink (old ureterostomy site)
Urethrostomy
Transureteroureterostomy
Nephropexy downward
Bladder tacked to sacral promontory
Heinecke-Mikulicz to kink
E
F
G
H

Fig. 17b. (E) Preoperative anatomy. (F) Operative reconstruction, made possible by sliding kidneys downward. (G) Antegrade pyelogram two weeks postoperatively. (H) Patient one month postoperatively.

Comment

Direct reconstruction in this case was made possible by mobilizing the kidneys which were tethered upward by his prior nephrostomies. If the left ureter had not reached the bladder, a segment of tapered ileum would have been employed as a lower ureteral substitute.

In our own experience with lower ureteral tapering we have encountered loss of blood supply of the lower ureter only in cases where the upper ureter was previously operated, as it was in this case. We believe, therefore, that it is safer to operate on the lower ureter first while its upper blood supply is intact.

Case 13. (Fig. 18) This little girl was referred in April 1972, at age 9½ years for possible urinary reconstruction. At age five weeks investigation for failure to thrive showed massive hydronephrosis of a solitary right kidney (Fig. 18a). Attempted pyeloplasty was unsuccessful, and a nephrostomy tube was inserted. Although clinically she did amazingly well considering the enormous hydronephrosis once present, there was low grade bacilluria even on appropriate suppressive medication. Investigation on admission (Fig. 18b) showed ureteropelvic junction obstruction and a ureter below which was small from disuse. The bladder was small, there was vesicoureteral reflux, but sensation seemed to be satisfactory. Operation (Fig. 18c) consisted of dismembering pyeloplasty, with reduction in size of the renal pelvis. At this same procedure during cystoscopy an attempt was made to hydrostatically dilate the bladder, and it ruptured! The rent was sutured. Nephrostogram postoperatively (Fig. 18d) showed satisfactory drainage to a tiny bladder; the tube was removed. Initially she voided frequently in small amounts, but this soon became normal. Intravenous pyelogram (Fig. 18e) six months postoperatively showed excellent function and less upper tract dilatation, as well as a bladder of normal size. It was hoped that her reflux might disappear with gradual enlargement of the bladder, but it did not, and so seven months after her upper tract repair, the ureter was reimplanted, which successfully stopped her reflux (Fig. 18c).

The patient (Fig. 18f) is now two years following reconstruction. The urine is sterile, creatinine 1.0 mg% and BUN 14 mg% and clearance 35 L absolute.

Comment

Although nephrostomy can be life saving in the acute situation, its long term use is complicated by chronic infection and often stone formation. It should be avoided whenever possible in childhood. This case demonstrates the often astounding degree of recovery possible with hydronephrosis in childhood after relief of obstruction. Assessing her original I.V.P. as a neonate, one would scarcely predict satisfactory renal function for this youngster almost 12 years later.

Discussion

Major reconstructive urinary surgery of infants and children, particularly after previous urinary diversion, can be very complex and difficult. To accomplish these reconstructions with success one must have ample background in various reconstructive procedures in order to select the best alternative for the individual case. Technical aspects of this surgery must be done precisely with respect to blood supply, reimplantation of ureters without angulation, and avoidance of reflux. The learning period of any individual surgeon is longer in this type of work than in straightforward cases such as ureteral reimplantation, because these cases are not so common in numbers and they differ substantially one from another. With some sense of apology and reticence, I believe that these cases should be relegated, at least for the present time, to those relatively few surgeons in each region whose practice affords a large and continuing experience in major reconstructive pediatric urology. Otherwise many of these children will end up with a permanent urinary diversion which is certainly second best to an intact urinary tract. A close parallel can be seen in the development of cardiac surgery of infants and children. Until 35 years ago none was performed. There then followed corrective surgery for the simplest malformations such as patent ductus arteriosus and coarctation of the aorta (i.e. simple ureteral reimplantation). Next came palliative surgery for certain complex conditions, such as pulmonary artery banding for ventricular septal defect, and pulmonary-systemic shunts for blue babies (i.e. loop ureterostomy, vesicostomy, etc.). Then came intracardiac correction of complex anomalies, including their repair in infants (i.e. definitive corrective surgery of complex urinary pathology). Although the results of successful correction were excellent, mortality was forbidding initially in many cardiac anomalies, until a relatively small number of surgeons concentrated on this work, gaining large experience with these complex problems. Ultimately referral channels directed these cases to those surgeons with special interest and skill in these problems, so that current results are very acceptable in pediatric cardiac surgery.

We believe that many children are subjected to urinary diversion who could instead be treated by direct reconstruction. Our experience with undiversion leads us to the conclusion that many previously diverted cases can be refunctionalized if bladder innervation is intact.

Some of these children will ultimately require transplantation, since in some the kidneys are dysplastic at birth and in others damage is severe at the first clinical presentation. We believe that even these children should be considered for refunctionalization because: 1) the quality of life will be better in those years before transplantation; 2) it is easier to maintain sterility in a closed urinary tract; and 3) a patient with a functioning bladder is a more suitable candidate for transplantation than one with a diversion.

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DISCUSSION

DR. ROBERT E. GROSS (Boston): Obviously, what has been done here required a good deal of initiative, clear thinking, and high technical skill in revamping the urinary systems of some of these unfortunate children and getting them back to near normalcy. As one looks at the field of urological problems in infancy and childhood over the last 20 or 30 years, tremendous advances have been made in correction of many of the anomalies we have seen. On the other hand, there are a considerable number of malformations, or combinations of different defects, which baffle us. We have operated hoping to improve things; very often we have ended up by doing two or three operations to try to get things better, and in the end, being somewhat overawed by the whole business, have turned—reluctantly, but, we thought, with good advice—to some sort of permanent external drainage of the urine, believing that this gave the best hope for recovery of damaged kidneys and longer life for the individual.

It's very refreshing to now see that many of these things which we did in the past in good faith can now be transformed, and patients turned to normalcy, or near normalcy.

As I get to the end of an academic surgical career, it has been a tremendous satisfaction to me on many occasions to find young men who have been through the residency training program and on our staff who have taken a new look at things in this field, and other areas in children's surgery, and with vision and thought have made new approaches and new techniques. They have accomplished things which we thought before were impossible. It's a great pleasure to let them have the ball and go toward new goals and get far ahead of us.

As I reflect on these things, it is very appropriate to recall the words, uttered so long ago by Leonardo da Vinci when he said: "The brilliant student will certainly outshine his teacher."

DR. VICTOR F. MARSHALL (New York): One of the first problems to be decided in whether you are going to reconstitute the urinary tract is: How good is the patient's urinary control likely to be if you have a success? Now, this almost automatically eliminates the myelomeningoceles, for example—not a small portion of the patients in our practice. Control is a great prize, and it is worthy of very strenuous efforts; but in some instances you just can't get it, no matter what.

A second problem to be faced is: Will the patient himself and his urinary tract be able to withstand a failure? These patients have already had some sort of a failure, sometimes very severe. The best laid plans and abilities do sometimes fail, and especially so in complex situations.

In passing, I agree with Dr. Hendren's reluctance to perform a "knuckle" cutaneous ureterostomy in continuity.

Since we have had some good results in other types of cases, some in children, with autotransplantations, we would seriously consider this procedure to bridge these gaps. Dr. Hendren has thought about it.

I wonder if Dr. Hendren would provide us with any guidelines as to which defunctionalized bladders would respond with a good capacity, and any sort of indication as to when they might respond. Some respond beautifully and at once, but some don't ever respond to get up to a reasonably good size. Would some kind of a bladder biopsy be of help?

DR. WILLARD E. GOODWIN (Los Angeles): There are several points to be emphasized. I certainly agree with Dr. Hendren's last point; that it is better to live without a bag on the skin.

The defunctionalized bladder will usually expand with use, but not always; and it may sometimes be necessary to augment the bladder with intestine.

In my view, the "tailoring" of the ileum is not necessary. We have a number of patients with an "ileal ureter" which works very well without tailoring.

(Slide) It is probably not necessary to do an antireflux procedure when ileum is used; but if this is desired, it can be done by intussusception, an old technique in surgery. Here is an experiment that Rod Turner and I reported in 1959. This shows a cystogram in a dog after an intussusception valve in a segment of ileum. You see there is no reflux.

(Slide) I should like to emphasize that time is important and a long followup should be stressed.

(Slide) Here is a little boy with what amounted to a solitary left kidney who was doomed to permanent nephrostomy after two unsuccessful attempts to fix the ureteropelvic junction. In 1965 we replaced the ureter with ileum and here is the postoperative intravenous urogram and postoperative cystogram showing that there is some reflux, but not very much under low pressure because it is a low pressure system. If these patients void frequently, I don't think it significant.

I should like to show with a motion picture what the cystoscopist sees when looking inside one of these segments of ileum. This happens to be a patient with papillary tumors in his kidney. Thus it is possible to look around inside the urinary tract, which is sometimes quite interesting.

(Slide) These diagrams are from Gil-Vernet, a famous Spanish urological surgeon who pioneered the use of ileum and cecum in order to bridge gaps in reconstruction of the urinary tract and enlargement of the bladder.

(Slide) This shows a summary of experiences with this ileocecocystoplasty in one of my own patients. This young lady has been followed from 1962 to the present. First she was wearing a suprapubic tube ever since childhood. It was later converted to a cutaneous diversion by Bricker's operation, and finally she had an ileocecocystoplasty. Here is the cystogram after this procedure. It shows the cecum attached to the dome of the bladder and that the ileocecal valve prevents reflux into the urinary tract in this particular case.

(Slide) Here she is herself. Her blood chemistries are normal. She is healthy. You can see how a pretty girl like this would prefer not to wear an external cutaneous urinary collecting device.

Dr. John Joseph Murphy (Philadelphia): I note that 17 of Dr. Hendren's 32 patients had valves as their initial problem, and I want to speak about the valves. The urologic surgeon who first encountered these patients cannot be blamed for diverting them, when you look at the roentgen evidence that he had.

(Slide) This is the excretory urogram of a child with posterior urethral valves, a rather appalling sight. And when you consider what an excellent roentgenographic result he can obtain by something like a cutaneous ureterostomy, you can't blame him for going to diversion early on.

My concern is that perhaps in some instances we are treating the roentgenograms rather than the patient.

Many of these children with valves are in very good clinical condition, and will tolerate, as an initial procedure, a direct attack on the obstructing lesion. Dr. John Duckett at our Children's Hospital of Philadelphia has used this approach in 26 children in the past three years, and the results have been extremely rewarding. Ten of these children have required no other surgical therapy.

(Slide) Here is an example of one of these children. The voiding cystourethrogram is on your left, the excretory urogram in the middle, and the postoperative appearance a year after resection of the valve.

(Slide) Finally, another such typical valve, an awful-looking upper tract, and a year later, after a simple resection of the valve, a normal pyelogram.

Apparently we may prevent and avoid diversion if we are selective about our patients, and attack the valve primarily.

Dr. John Lilly (Denver): We are in total agreement with Dr. Hendren's basic premise; that is, conservation of natural urological anatomy. This goal may be reached by several different methods, and I'd like to point out another technique, which, by taking advantage of knowledge in related areas, may avoid the necessity for urinary diversion in the first place.

Occasionally, after attempts at ureteral reconstruction in these children, the kidney and a fairly good proximal ureter are joined to the bladder by a fibrotic, aperistaltic, unsalvageable distal ureter. An ileal diversion would seem the obvious answer. We believe a preferable alternative is to excise the distal ureter and then transfer the kidney close enough to permit a comfortable reimplantation of the proximal ureter into the bladder. I have two pertinent slides.

(Slide) This is the IVP in a 6-year-old boy we recently cared for at the University of Colorado. He had had posterior urethral valves, high cutaneous ureterostomies, two attempts at ureteroneocystostomy, and now after multiple reconstructive procedures, massive ureteral reflux into his only remaining good kidney. The ureter distal to the previous cutaneous ureterostomy was a worthless mass of scar tissue. We excised the kidney, perfused it outside the body, and then revascularized it in the pelvis by standard transplant techniques. (Slide) In this instance the anastomosis of the renal artery was to the aorta, and the renal vein anastomosis was to the common iliac vein.

The fibrotic distal ureter was now redundant and was excised. The proximal ureter was easily reimplanted. This child is well two months after his surgery, and is the tenth in a series of renal autotransplants at our institution.

We believe autotransplantation is another feasible maneuver in our efforts to preserve natural function of the urinary tract.

Dr. J. Hartwell Harrison (Boston): I think it quite appropriate after this wonderful presentation of Dr. Hendren's to pay tribute from the American Board of Urology and the American Urological Association for the contributions of the late W. E. Ladd, the late Thomas Lanman, Bob Gross, and now Hardy Hendren, for all they have done to establish and advance pediatric urology; and I'm sure that my colleagues join me in this congratulation to Hardy Hendren and his teachers. Our residents have profited greatly by their association with him. I'd like to emphasize the implications of his work in the field of renal transplantation, both with reference to refunctionalization of the bladder and preservation of the blood supply of the ureter.

Dr. Hendren, I think it might be appropriate to ask you one question about the evolution of surgical education, and that is: Today, is it time for children's hospitals to have divisions of urology?

Dr. W. Hardy Hendren (Closing discussion): First, to my teacher, Dr. Gross, let me say that none of your many pupils believe that they will outshine their mentor. Dr. Marshall has raised some interesting points. We have not attempted undiversion in any case where the problem was neurogenic bladder. We do not think these children are reconstructable by the techniques presented today. However, recent efforts by Dr. F. Brantly Scott of Houston, and others, may improve the outlook for those children.

It is not possible to adequately test the bladder function preoperatively in a child who has had diversion for many years. About the best that we can do is to fill the bladder slowly while observing it fluoroscopically. This gives an assessment of sensation. Most of these youngsters in our experience do not know what to do initially when we ask them to void, although some of them do it immediately on request. The majority of these bladders are very small from long standing disuse. They stretch up to a reasonable capacity very soon after refunctionalization, however. Two recent reports, one by Mr. D. I. Williams of London, and another by Dr. E. A. Tanagho of San Francisco have emphasized that some of these long diverted, contracted bladders, may never work in a satisfactory manner. To this date we have not encountered any whose bladder function proved entirely unsatisfactory, although some have been better than others. I believe it is reasonable in these children, who do not have any stigmata that would suggest neurological dysfunction of the bladder, to hook them up and hope for the best. Obviously they must be followed very carefully so that if deteriorization of function should occur, another approach could be followed.

Dr. Marshall, and also Dr. Lilly, have referred to the possibility of autotransplantation. I have not been bold enough to do that in this particular group of children for several reasons. First, they generally have limited renal function, which was why they were diverted in the first place. It seems to me that autotransplantation poses a greater risk than some of the other alternatives employed. Not infrequently, the urinary tract is not sterile when we are doing these undiversion procedures, and we would prefer to avoid doing a vascular anastomosis in that situation. We would, on the other hand, be quite prepared to do autotransplantation of the kidney in a child in other selected clinical circumstances, such as renal vascular hypertension with involvement of the mid-abdominal aorta.

We all owe a great debt to Dr. Goodwin because he has been one of the pioneers in this field. He has long emphasized that one should not give up easily and resort to permanent urinary diversion. With some of his own cases this morning and previously in the literature, he has underscored that the surgeon must be resourceful and do the best that he can with the anatomy at hand. Possibly Dr. Goodwin may be correct that perhaps it is not necessary to tailor the conduits as we have done, but that has seemed to us desirable from two standpoints. First, as we have studied some of these underdiverted ileal loop cases, the segment of the loop which had been tapered appeared to propel urine much more effectively into the bladder than a bowel of normal caliber. We know that a megaureter which cannot coapt its walls does not deliver urine to the bladder as effectively as a ureter of normal size. Secondly, tailoring reduces the absorptive surface of bowel mucosa which is an important point in a patient with already reduced renal function. In one of our patients there was a very significant increase in measured creatinine clearance after tapering the upper half of a conduit in which only the lower end had been tapered at the time it was reconnected to the bladder. And thirdly, by tailoring the segment of bowel, we can achieve an effective reimplantation with a nonrefluxing tunnel in the trigone of the bladder. We know that reflux to the kidney is often harmful. It seems reasonable therefore to conclude that a technique which avoids that must be better than one in which reflux occurs even if the bowel segment empties it back down to the bladder quickly.

Dr. Murphy has raised some interesting points about urethral valves, and I certainly agree with much of what he has said. As we have emphasized previously, urethral valves are a congenital malformation, and all congenital malformations occur in a spectrum of severity. At one end of the spectrum are mild cases, and at the other very severe cases in renal failure. In some instances we do just a transurethral resection and watch them for a long time, without doing any other major reconstructive procedure. I believe, that in the very severe cases they frequently need to have something more done. It is our belief that those very severe cases can be directly reconstructed rather than doing a temporary diversion which has been practiced so widely in the past decade. As we look at the literature on this subject, we find that many of these so called temporary diversions are not temporary at all, but that the child remains with it permanently. It was of interest last evening to hear the remarks by Mr. Eoin Aberdeen who emphasized that results of early complete correction of certain infants with complex cardiac malformations is preferred to a temporizing approach.

Dr. Harrison has brought into focus the important question of how should we teach pediatric urology. We cannot decide that issue here and now but perhaps a few general remarks are in order. Pediatric urology, which constitutes possibly a third of the surgery of infants and children, has emerged as a special field of endeavor. There is a great need for a number of men throughout the country to take special interest in this field, just as has occurred in cardiac surgery and in other types of pediatric surgery. Much of pediatric urology is very difficult, technically demanding surgery and results will obviously be better in the hands of those who devote much of their time and energy to it. I believe we must gear our residency programs to train those surgeons who are interested in this field, whether they come from parent programs in urology or from pediatric surgery. It is time we stopped having jurisdictional disputes as to who owns the patients and get together to work at doing a better job for these children. There are many more of these children who need good surgical attention than there are currently surgeons who are skilled in doing it.

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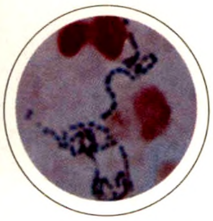
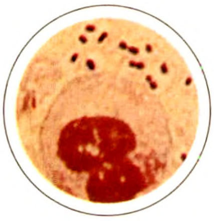
Staphylococci —(*Staphylococcus aureus* and *S. epidermidis* including both penicillinase- and non-penicillinase-producing strains.)

Septicemia, infections of soft tissue, skin, upper and lower respiratory tract.

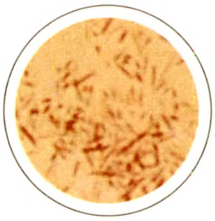


Streptococci—(Streptococci except *Streptococcus faecalis.*)

Septicemia, infections of soft tissue, skin, upper and lower respiratory tract. (Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. Cleocin PO_4 is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cleocin PO_4 in the subsequent prevention of rheumatic fever are not available at present.)



Pneumococci —Upper and lower respiratory infections.



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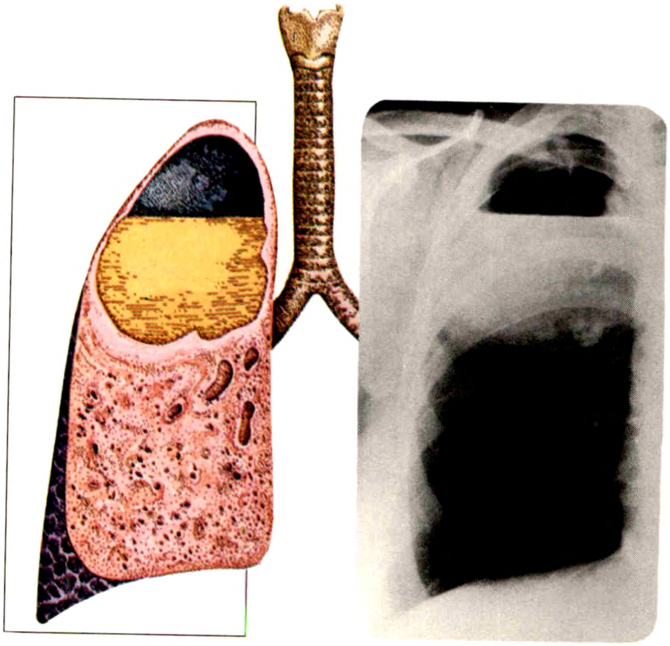
A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Useful as initial therapy... with a bonus. Cleocin PO_4 is indicated for more than the treatment of susceptible gram-positive organisms.** It has the bonus of activity against anaerobes. For these obscure and potentially lethal pathogens, it may merit early consideration.

Anaerobes: ubiquitous opportunists. Anaerobes are the dominant population group among the resident flora of the human body. They are abundant in the oropharynx, female genital tract, and in the gut where they constitute 95% of normal fecal flora, out-numbering *Escherichia coli* 1,000 to 1.

Except for *Clostridium*, which became notorious during World War I, anaerobes have often been dismissed as harmless saprophytes. Only recently have they begun to be recognized as a major source of serious infection.

When trauma, surgery, or weakened bodily defenses allow them to spill into the peritoneal cavity, or invade the bloodstream or compromised tissue, they can become lethal opportunists.



When the medium has no message. Anaerobes are the most easily missed category of potentially pathogenic bacteria. Often their presence can only be inferred when a lesion that shows abundant bacteria on a Gram-stained slide yields an apparently sterile culture with routine aerobic methods.

Anaerobes require meticulous collection and special culture techniques. Even a brief exposure to air can kill many of them. Most are fastidious, and they may require as much as ten days' incubation to reveal their presence. In some busy laboratories, plates are discarded prematurely; in others, anaerobic cultures are rarely even made.

The problem of Bacteroides. *Bacteroides* are the most numerous of the anaerobic bacteria and the ones most frequently found in clinically significant anaerobic infections. *Bacteroides* species have been identified in approximately half of surgical infections caused by anaerobic organisms.

Although most *Bacteroides* species are sensitive to penicillin, a frequent exception is *Bacteroides fragilis*—the most commonly encountered pathogen in the genus. This, the most prevalent of anaerobic pathogens, has remained the most difficult to eradicate. Despite antibiotic therapy, *Bacteroides* septicemia has proved fatal in 30% to 40% of patients afflicted.

**Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and its long-term prophylaxis of rheumatic fever.

For further prescribing information, please see last page of this advertisement.
A complete bibliography is available from The Upjohn Company.

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and anaerobes*

pathogens indicated above

Improving the odds against anaerobes. In anaerobic infections the therapeutic significance of Cleocin PO_4 (clindamycin phosphate injection) is best recognized in the context of the seriousness of many of the infections successfully treated. All but one of the clinically and bacteriologically evaluatable patients in the pre-introductory study group had moderate to severe infections. Most had one or more complicating illnesses and, in many, host defenses were severely compromised by traumatic injuries, neoplastic disease, or radical surgery.

Anaerobic infections developed in many as a sequel to massive abdominal gunshot or stab wounds, multiple fractures, or surgery of the gastrointestinal or female genital tract.

Clinical diagnoses included septicemia, deep abscesses of the lungs and various sites in the abdominal cavity and female genital tract, and cases of peritonitis, empyema, endometritis, postsurgical vaginal-cuff infections and anaerobic pneumonitis. In many cases multiple antibiotic regimens, alone or in combination, had failed to control the infection before Cleocin PO_4 therapy was initiated.

Serum levels of clindamycin above the *in vitro* minimum inhibitory concentration for most indicated organisms can be readily achieved and maintained. The minimum inhibitory concentration *in vitro* for anaerobes is generally 1.6 mcg/ml or less.

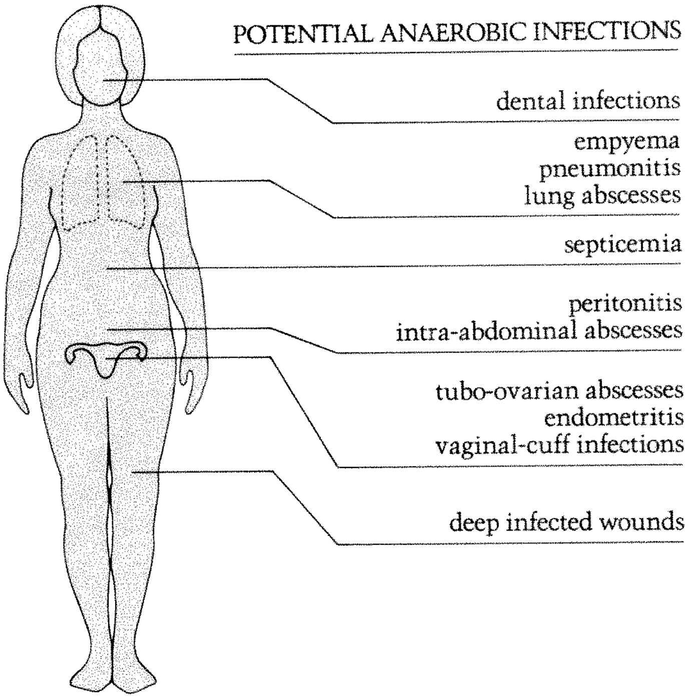
When you suspect an anaerobe. Cleocin PO_4 (clindamycin phosphate injection) is demonstrably effective in anaerobic infections. But with or without the availability of effective antibiotics, the principal problem in managing these infections is recognizing them.

A questioning mind and a sensitive nose are the first and second prerequisites, respectively. Deep necrotic lesions are a potential breeding ground for anaerobes, particularly if located near the oropharynx, the female genital tract, or the gut. Contamination from these areas enhances the risk of infection, as does compromised host resistance. A foul or fecal-smelling lesion or exudate suggests anaerobic infection. Organisms that are visible on the Gram-stained slide but fail to grow on conventional aerobic culture media may be anaerobes.

As with any infection, specimens for culturing and susceptibility testing should be collected before therapy begins. At present, since disc susceptibility testing with present methods is not reliable for anaerobes, *in vitro* dilution methods should be used to determine susceptibility. In severe anaerobic infections, treatment may be started before a definitive diagnosis is made.

If it's a gram-positive coccal infection, there are several alternatives.

If you suspect an anaerobe, consider Cleocin PO_4.



Predictable serum levels... predictably maintained. Cleocin PO_4 is a water-soluble ester of clindamycin and phosphoric acid which hydrolyzes into biologically active clindamycin base within minutes of infusion. Peak serum concentrations of active antibiotic are reached in ten minutes following a 300 mg intravenous dose. With intra-muscular administration, peak levels are achieved within three hours in adults and one hour in children.

Serum levels of clindamycin above the *in vitro* minimum inhibitory concentrations for most indicated organisms can be maintained by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children, or by continuous intravenous infusion.

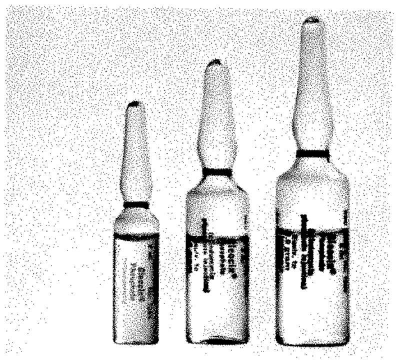
Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease. However, patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy. Elevations of serum transaminases have been observed during therapy with Cleocin PO_4 (clindamycin phosphate injection).

Cleocin PO_4 should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the Dosage and Administration section of the prescribing information.

STERILE SOLUTION ●

Cleocin® PO4

clindamycin phosphate injection, Upjohn



Effective parenteral therapy against susceptible gram-positive cocci and anaerobes

WARNING

Severe and persistent diarrhea, which may be accompanied by blood and mucus, and which may be associated with changes in large bowel mucosa diagnosed as "pseudomembranous colitis" has been reported in association with the administration of Cleocin Phosphate (clindamycin phosphate).

When significant diarrhea occurs (usually more than 5 bowel movements daily), the drug should be discontinued or, if necessary, continued only with close observation of the patient (large bowel endoscopy has been recommended). Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte and protein supplementation as indicated. Antiperistaltic agents—opiates, meperidine, and diphenoxylate with atropine may prolong and/or worsen the condition. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

Note: Diarrhea has been observed to begin up to several weeks following cessation of therapy with Cleocin Phosphate. The physician must be alert to this possibility.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Cleocin Phosphate is indicated in the treatment of infections caused by susceptible strains of the following micro-organisms:

Streptococci: Upper respiratory tract infections (Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. Cleocin Phosphate is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cleocin Phosphate in the subsequent prevention of rheumatic fever are not available at present.); lower respiratory tract infections; skin and soft tissue infections; septicemia.

Staphylococci: Upper and lower respiratory tract infections; skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Upper and lower respiratory tract infections.

Anaerobic bacteria: Lower respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; skin and soft tissue infections; septicemia; intra-abdominal infections, such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract, such as endometritis, non-gonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Adjunctive Therapy: In dental infections and in the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings (See WARNING box)

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro.* Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established. *Usage in Newborns and Infants:* When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of non-susceptible organisms, particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

How Supplied: Cleocin Phosphate (clindamycin phosphate) available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base.

Ampoules of 2, 4 and 6 ml.

Caution: Federal law prohibits dispensing without prescription.

For additional product information see your Upjohn representative.

MED B-3-S (NDT) J-4245-9

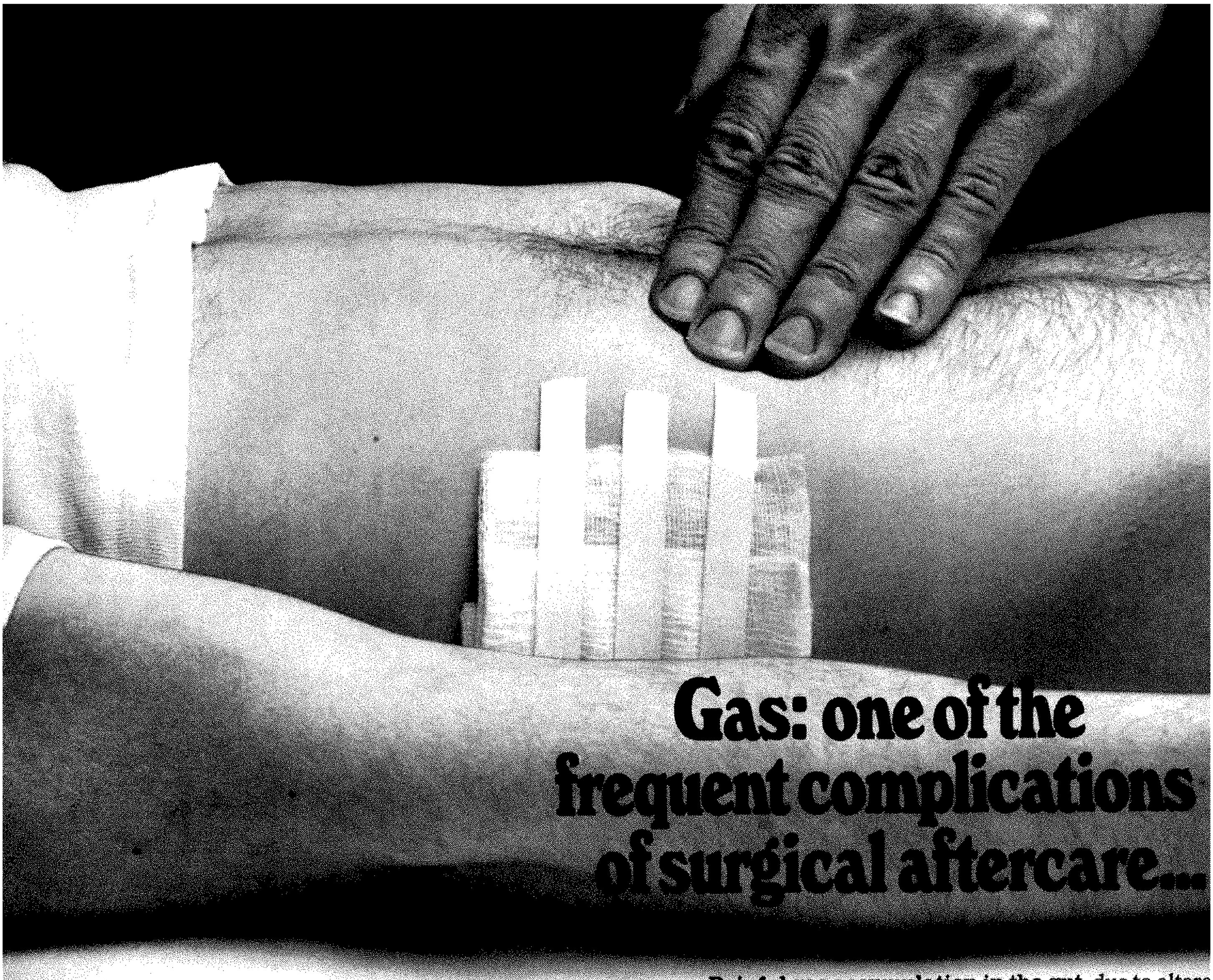
STERILE SOLUTION

Cleocin® PO4

clindamycin phosphate injection, Upjohn

FOR INTRAVENOUS AND INTRAMUSCULAR USE

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001


Gas: one of the frequent complications of surgical aftercare...

Painful gas accumulation in the gut, due to altere intestinal motility, aerophagia and increased salivation, often complicates surgical aftercare.

To help avoid or dispel the acute discomforts of post-op pain in the gut, Phazyme provides simethicone, *"... an effective, safe and simple method of preventing abdominal distention, gas pain and reducing the incidence of ileus."*[1]*

Phazyme's unique dual-phase action releases 20 mg. of specially-activated simethicone initially to the stomach for immediate dispersion of entrapped g

The protected inner core delivers an additional 40 mg. of specially-activated simethicone to relieve pain of entrapped gas throughout the lower G.I. tract.

Phazyme also provides 240 mg. of pancreatin directly to the small intestine to help assure normal digestion.

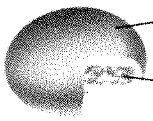
And Phazyme is safe ... no systemic effects ... no untoward reactions ... no contraindications other than known allergy to an ingredient.

1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol. 38*:386, Sept. 1971.
*Italics ours.

Phazyme®

Reed & Carnrick/Kenilworth, N.J. 07033

prevents and relieves pain due to entrapped gas



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Complete Product Information—Approved Official Package Insert

DESCRIPTION DEXON® polyglycolic acid Suture—Synthetic, Absorbable is a homopolymer of glycolic acid. The sutures are sterile, inert, noncollagenous, nonantigenic, nonpyrogenic, flexible, braided, undyed, with a natural beige color. They are uniform in size and tensile strength, but are smaller in diameter than Absorbable Surgical Sutures of equivalent tensile strength.

ACTIONS When DEXON is placed in tissues a minimal tissue reaction occurs, which is followed by a microscopic layer of fibrous connective tissue which grows into the suture material. Animal studies (subcutaneous tissue in rats, rabbits and dogs) revealed minimal absorption at 7 to 15 days, significant absorption at 30 days, and maximum resorption after 60 to 90 days. Tensile strength, not being a function of the absorption rate, may vary from tissue to tissue, depending in part on the rate of hydrolysis. The early tensile strength of DEXON is reported to be greater than that of comparable chromic catgut. In animal studies (subcutaneous tissue of rats, rabbits and dogs) there occurred a 30 to 50% loss of initial tensile strength in one week and 60 to 80% loss in two weeks, at which time as in the case with chromic catgut no useful residual tensile strength remains.

INDICATIONS DEXON sutures are indicated whenever absorbable sutures and ligatures are employed, provided that extended approximation of tissues is not required or where undue postoperative tension or stress is not anticipated. DEXON is also indicated where non-absorbable sutures are used for their characteristic lack of tissue reaction.

CONTRAINDICATIONS DEXON is contraindicated where extended approximation of tissues under strain must be maintained.

WARNINGS The safe use of this suture in cardiovascular, neural and ophthalmological surgery has not been established. Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon. Do not resterilize. Discard opened, unused sutures.

PRECAUTIONS Acceptable surgical practice should be followed with respect to drainage and closure of infected wounds. DEXON suture knots must be properly placed to be secure. Therefore, place first throw in precise position for final knot, using a double loop, tie second throw square using horizontal tension; additional throws may be used as desired. Skin sutures which remain in place for periods of longer than seven days may cause localized topical irritation and the extended portion of suture may be snipped off after five to seven days, as indicated.

ADVERSE REACTIONS Those reactions that have been reported include tissue reaction or inflammation, fibrous or granulation tissue, wound separation and bleeding and accumulation of fluid around subcuticular stitches.

DOSAGE AND ADMINISTRATION Use as required. Do not resterilize. Discard opened, unused sutures.

HOW SUPPLIED Suture sizes 6-0 through 1. Supplied in cut lengths or ligating reels, non-needled or affixed to the various DAVIS + GECK ATRAUMATIC® needles in three dozen packages. Rev. 6/73

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American Cyanamid Company
Pearl River, N.Y. 10965

The best salesmen for DEXON® polyglycolic acid suture don't work for us.

They're the surgeons who use it.

Surgeons in 60 countries have used DEXON sutures successfully in nearly every kind of surgical procedure. To date, these procedures number over 10,000,000.

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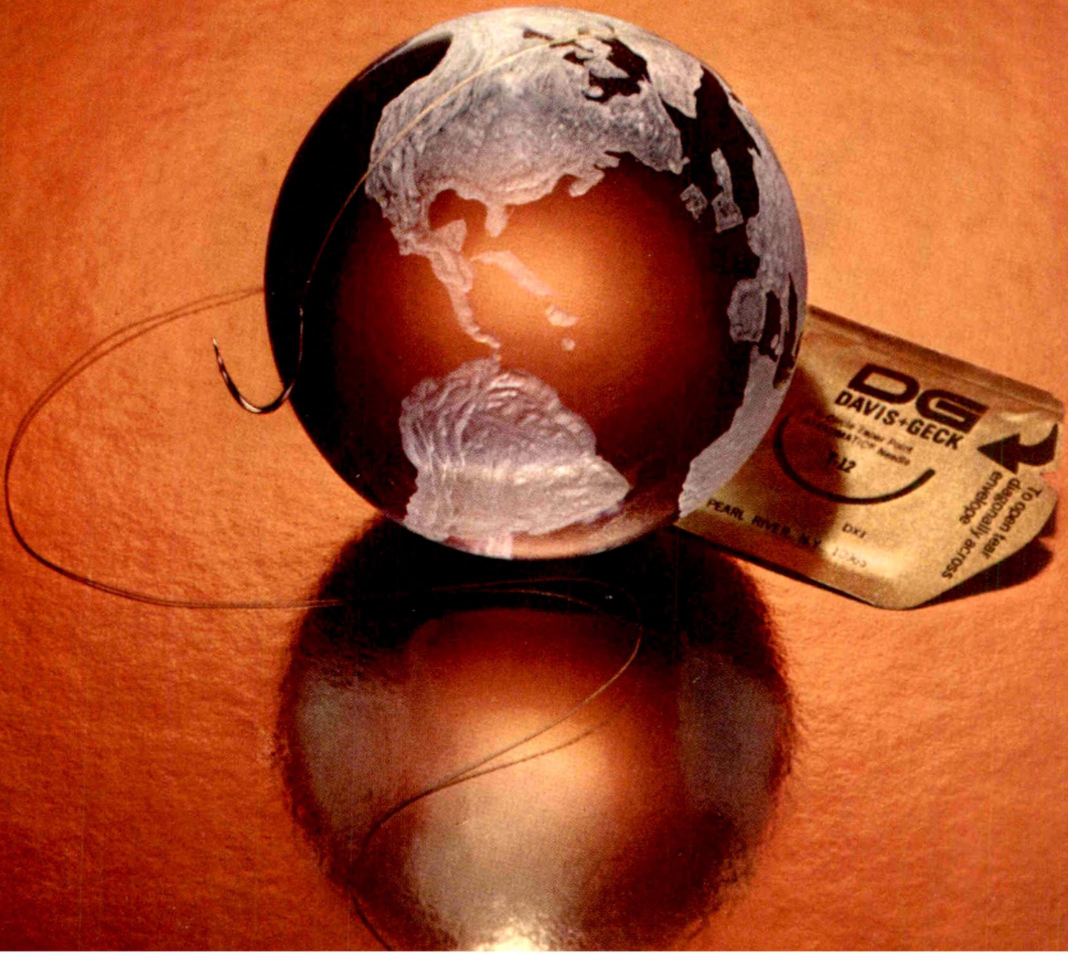
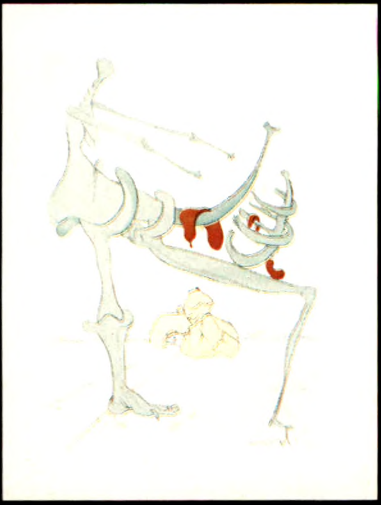
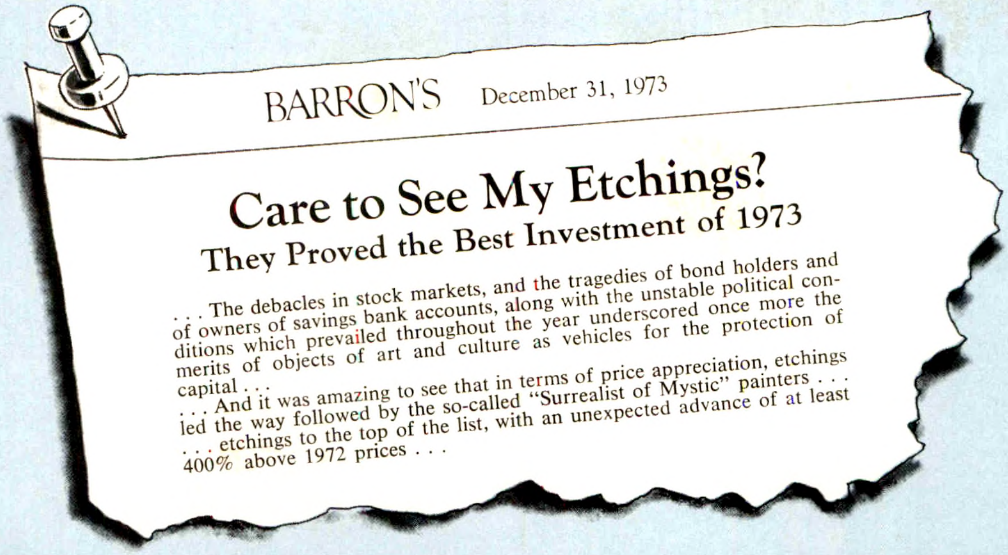


Jean-Paul Loup
exclusively presents
"Dalinian Fantasia"
by Salvador Dali



Actual size of each engraving: 26¼"x20".



BARRON'S December 31, 1973

Care to See My Etchings?

They Proved the Best Investment of 1973

. . . The debacles in stock markets, and the tragedies of bond holders and of owners of savings bank accounts, along with the unstable political conditions which prevailed throughout the year underscored once more the merits of objects of art and culture as vehicles for the protection of capital . . .

. . . And it was amazing to see that in terms of price appreciation, etchings led the way followed by the so-called "Surrealist of Mystic" painters . . . . . . etchings to the top of the list, with an unexpected advance of at least 400% above 1972 prices . . .

"DALINIAN FANTASIA" is a series of 6 ORIGINAL ENGRAVINGS by SALVADOR DALI, made on Papier Richard in a very limited, signed and numbered edition of 100.

A chance to acquire a Dali Original is a rare opportunity . . . A chance to acquire a series of SIX DALI ORIGINALS (that are among the surrealist master's favorites) has to be THE OPPORTUNTY OF A LIFETIME for any collector or investor. Since this series was completed, Dali has doubled his commissions. Thus never again will we be permitted to offer Dali originals of such quality at such a low figure!

Salvador Dali conceived these striking surrealistic works especially for the unique medium of Drypoint Engraving. Each one of these Original Engravings has been made on PAPIER RICHARD, a HANDMADE paper (probably the world's finest and most sought after paper). Each Original Engraving has been watercolored by hand (no printing ink used) with the help of a stencil done after the first series made by Dali himself. This method is called "POCHOIR," and is considered one of the very finest and hardest to execute.

Usually, to protect the value of such a limited edition, the original engraving copper plaques are destroyed when the edition is completed. However, after PERSONALLY EXAMINING, APPROVING, NUMBERING and SIGNING each of these prints, Salvador Dali felt that this work was so IMPORTANT, he donated the 6 plaques to the world famous DALI MUSEUM in Figueras, Spain, to be preserved and permanently displayed.

From an art standpoint, this has to be one of the finest exclusive offerings that Jean-Paul Loup has ever been privileged to make. Also, when you consider that the NUMBER ONE FINANCIAL WEEKLY MAGAZINE in the U.S. classified Original Engravings and Etchings by premier artists as THE BEST INVESTMENT OF 1973 . . . (it is said in the article that prices advanced by over 400% above 1972 prices) . . . the investment potential of this offering is equally rare.

"DALINIAN FANTASIA" is limited to only 100 series of 6 Original Engravings on Papier Richard. Most important, no artist's proofs exist.

This magnificent edition on Papier Richard is a Jean-Paul Loup exclusive and is not available anywhere else in the world. However, two other editions of LESSER IMPORTANCE, limited also to 100 numbered series each, were also made and are currently being sold in Europe for about 20% higher than our asking price.

As a matter of fact, this remarkable series of Salvador Dali Original Engravings may be purchased at this incredible low price only because you will be acquiring them directly from the Original Editor of Art, Jean-Paul Loup.

In the troubled financial scene where inflation makes your dollar worth less by the minute, and where most stocks and bonds are the cause of heartache, what other investment offers you such great growth potential? What other investment offers you such splendid potential (remember the 400% increase in the value of works of this kind) and provides such pleasure and pride of ownership? Just visualize SIX ORIGINAL SIGNED ENGRAVINGS BY SALVADOR DALI hanging in your home or office . . . each one as much an original work of art as a drawing, water color or oil painting.

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the low-back patient and his problems:

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Neck and shoulders rigid and tense
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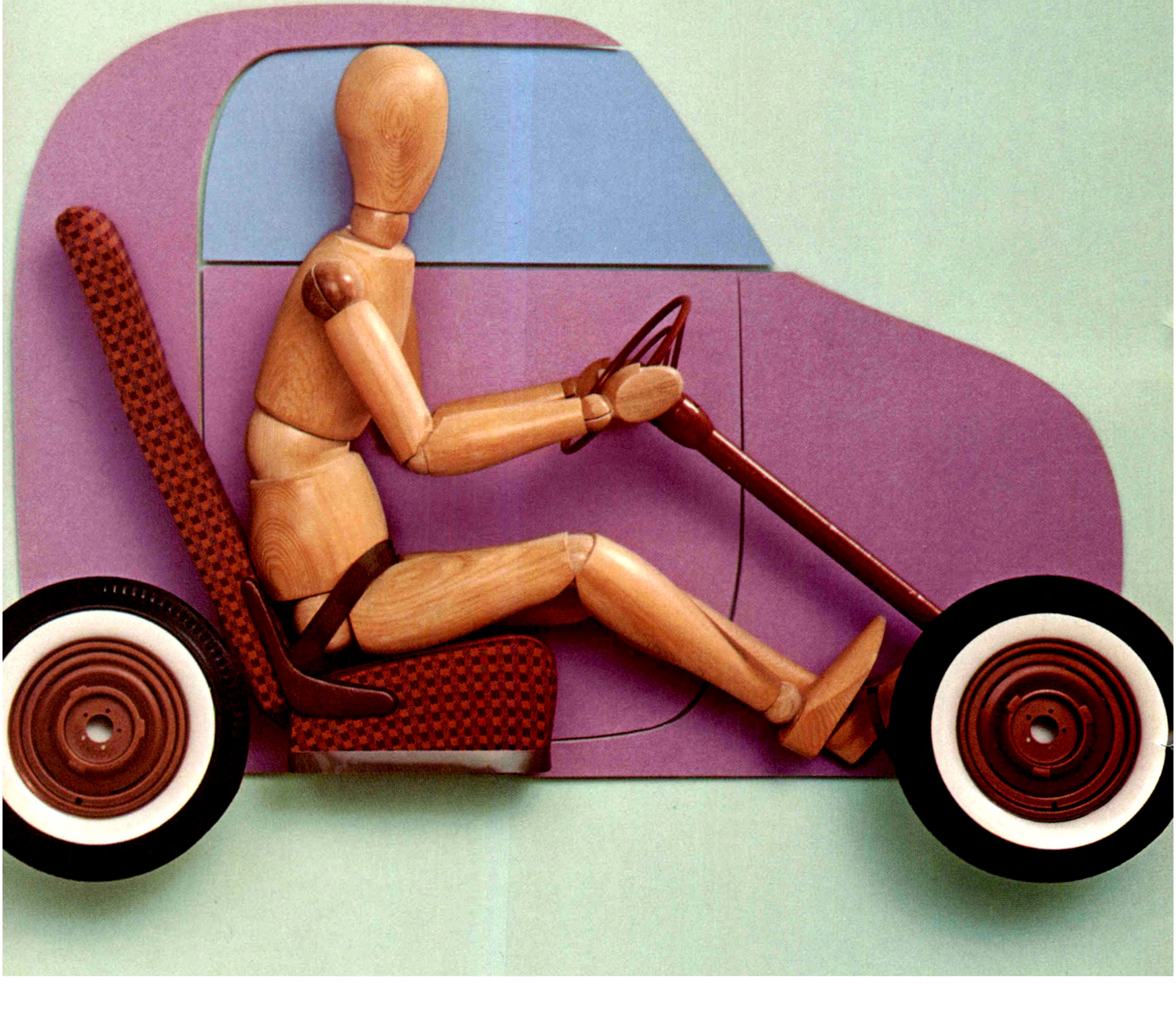

the solution:

Push front seat forward to reduce strain on back and shoulder muscles. Insert small cushion between small of back and rear of car seat. Back support can help relieve pain and fatigue. Always wear seat belt and shoulder harness. On long trips get out of car and stretch every couple of hours.

to treat acute musculoskeletal disorders...

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(methocarbamol)

750 mg. capsule-shaped tablets

the Robaxin® Regimen:

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To relieve the discomforts associated with acute musculoskeletal disorders, Robaxin®-750 is often indicated. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

See package insert for full prescribing information.

A.H. Robins Company, 1407 Cummings Drive, Richmond, Va. 23220
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Whenever an APC/narcotic is indicated.

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Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, Percodan is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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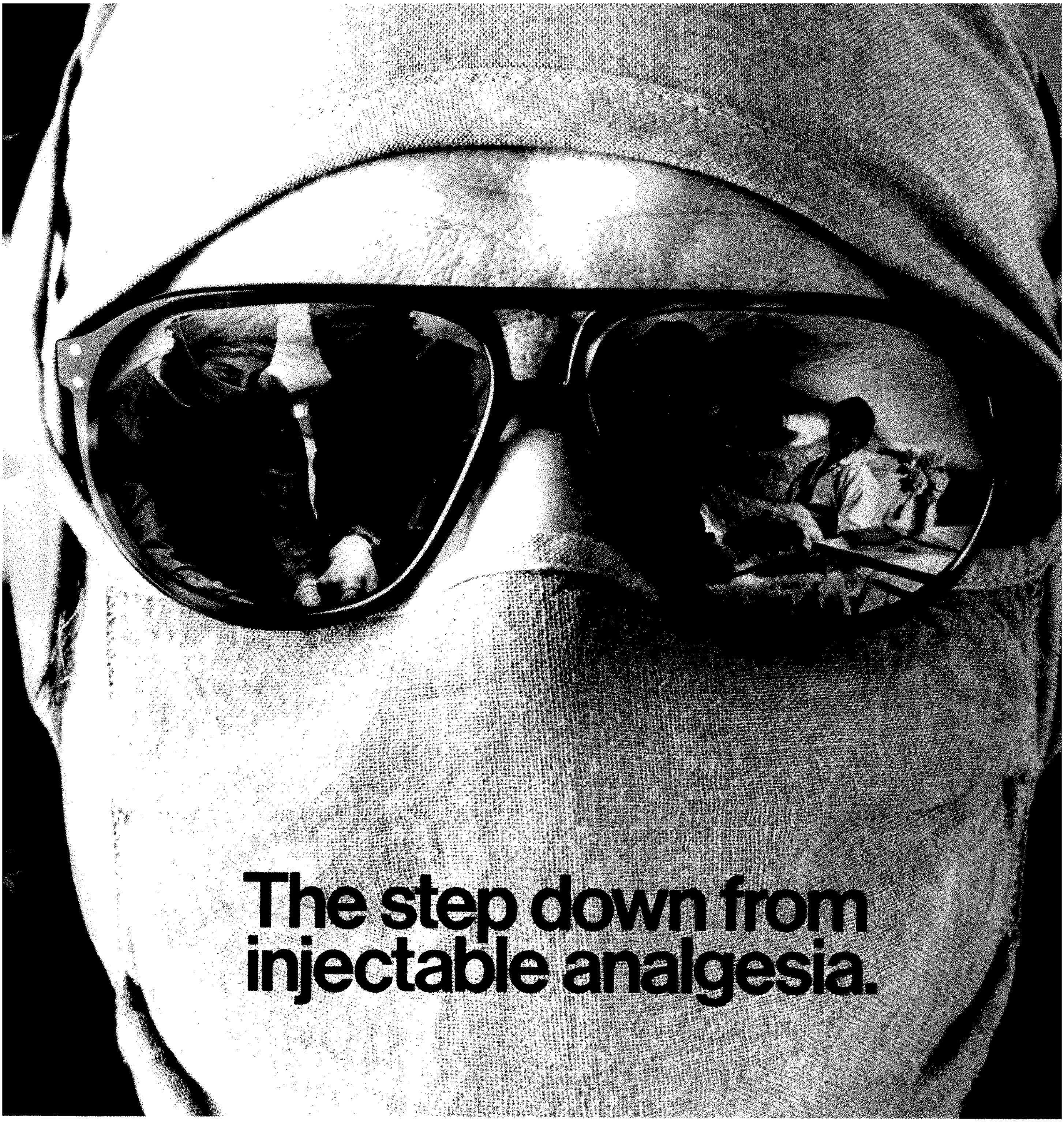

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☐ one tablet q.6 h.*
☐ oxycodone, the principal ingredient of Percodan, is one of the more readily absorbed oral narcotic analgesics
☐ helps afford pain-free sleep
☐ unit dose available

Tablets
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Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

See facing page for Brief Summary

*See dosage and administration section of Brief Summary

EN 6541

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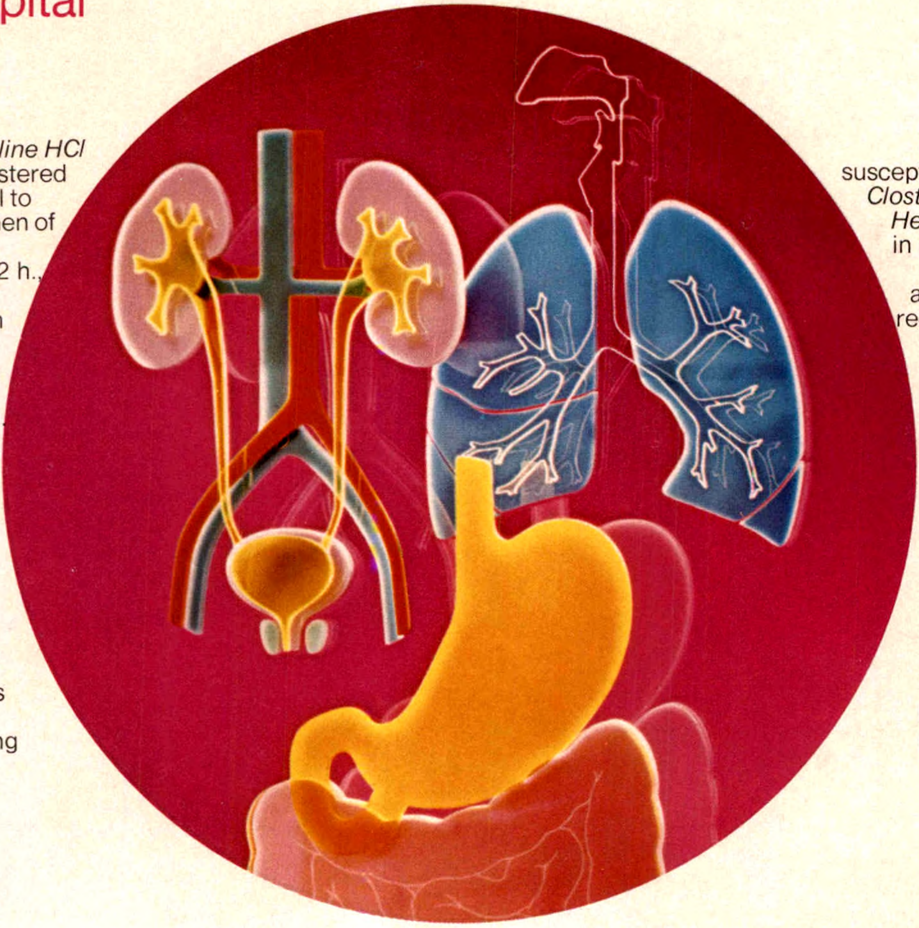

MINOCIN *Minocycline HCl* Intravenous administered in dosages identical to the usual oral regimen of MINOCIN, 200 mg initially, 100 mg q. 12 h., provides prompt antimicrobial serum levels to control infections caused by susceptible pathogens in the hospital.

MINOCIN can be effective in the treatment of pneumonia, skin and soft tissue infections, bacteremia and septicemia. In hospital infections, it can be useful against populations of pathogens assuming increasing importance, such as susceptible *Bacteroides* sp., *Clostridium* sp. and *Mima-Herellea* sp., implicated in postsurgical G.I. and G.U. infections; and against populations of recognized importance such as *E. coli* and *Klebsiella* sp. (See Table II.)

MINOCIN I.V. used as recommended rarely results in thrombophlebitis. If MINOCIN I.V. is given over prolonged periods, however, thrombophlebitis may occur. In all applicable cases, oral MINOCIN should be instituted as soon as possible.

*When bacteriologic testing indicates appropriate susceptibility to MINOCIN *Minocycline HCl*.

MINOCIN *Minocycline HCl* penetrates:*

APPENDIX	OVARY
BLADDER	PROSTATE
COLON	RECTUM
DUODENUM	STOMACH
FALLOPIAN TUBE	THYROID
GALLBLADDER	TONSIL
KIDNEY	UTERUS
LIVER	

*Penetration of Minocycline HCl has been shown to occur in several tissues of various organ sites obtained from biopsy specimens from surgical patients not undergoing specific therapy. Tissue penetration is regarded as essential to therapeutic efficacy but specific penetration levels have not been directly correlated with specific therapeutic effects.

TABLE II

PENETRATES SITES OF INFECTION TO OVERCOME SUSCEPTIBLE HOSPITAL PATHOGENS**

PATHOGEN***	SITES OF SURGERY/INFECTION (NOT INCLUSIVE)
Bacteroides sp.	Gallbladder Lower G.I. Tract Female G.U. Tract
Clostridium sp.	Gallbladder
E. coli	Prostate G.I. Tract G.U. Tract
Klebsiella sp.	Respiratory Tract G.U. Tract
D. pneumoniae	Respiratory Tract
Enterobacter (Aerobacter)	G.I. Tract G.U. Tract
H. influenzae	Respiratory Tract
Enterococcus	Lower Bowel G.I. Tract
Mima-Herellea sp.	Urethra Vaginal Tract
*Staphylococcus aureus*****	Skin and Soft Tissue

**When bacteriologic testing indicates appropriate susceptibility to MINOCIN *Minocycline HCl.*

***MINOCIN not active against *Proteus* sp. or *Pseudomonas.*

****Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infections. MINOCIN is indicated for treatment of *Staphylococcus aureus* in skin and soft tissue infections *only* when bacteriologic tests indicate appropriate susceptibility to the drug.

IN VITRO ACTIVITY† OF MINOCIN *Minocycline HCl* AGAINST 421 STRAINS OF VARIOUS BACTERIA, INCLUDING PATHOGENS AND NONPATHOGENS††

ORGANISM	NUMBER OF STRAINS TESTED	MINOCYCLINE ACTIVITY
Staphylococcus aureus	56	56
Diplococcus pneumoniae	35	31
Streptococcus, group A	63	57
Streptococcus, group B	12	6
Streptococcus, group C	3	3
Streptococcus, group G	3	3
Streptococcus viridans	31	30
Enterococcus	36	6
Neisseria gonorrhoeae	25	21
Hemophilus influenzae	15	1
Escherichia coli	48	32
Proteus sp.†††	34	3
Klebsiella	17	9
Enterobacter aerogenes	3	3
Enterobacter cloacae	7	3
Serratia	4	4
Herellea	7	7
Mima polymorpha	1	1
Pseudomonas aeruginosa	15	6
Providencia	3	
Bacillus cereus	3	

†No direct correlation should be inferred between *in vitro* and *in vivo* activity.

††No approved clinical indication for MINOCIN therapy in infections due to *Proteus* sp., *Pseudomonas, Providencia* and *Bacillus cereus.*

†††Includes two strains of *P. morganii* and *P. rettgeri* and 32 of *P. mirabilis.*

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Before prescribing MINOCIN, please refer to the prescribing information for full description of adverse effects and precautions, a copy of which is on the last page of this advertisement.

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MINOCIN provides effective therapy with relatively few problems

- Penetrates tissues of respiratory, G.I. and G.U. tracts, skin and muscle.
- No photosensitivity to date.
- Well absorbed even with food, dairy products or colas.
- Enamel hypoplasia/tooth staining can occur in children under eight.
- If renal impairment exists, lower than usual doses are indicated. (See WARNING in Package Insert.)
- Lightheadedness that may occur is transient, disappearing during therapy or always after therapy is completed.
- Dosage form flexibility: supplied as 50 mg and 100 mg capsules, 50 mg/5 cc syrup, and 100 mg/vial intravenous.

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MINOCIN® Minocycline Hydrochloride Oral and Intravenous

DESCRIPTION: MINOCIN *minocycline hydrochloride* is a semi-synthetic derivative of tetracycline. 7-dimethylamino-6-deoxy-6-demethyltetracycline hydrochloride.

Intravenous: Each vial, dried by cryodesiccation, contains sterile Minocycline Hydrochloride equivalent to 100 mg. Minocycline. When reconstituted with 5 cc. of Sterile Water For Injection the pH ranges from 2.0 to 2.8.

ACTIONS: Microbiology. The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Minocycline HCl is a tetracycline with antibacterial activity comparable to other tetracyclines with activity against a wide range of gram-negative and gram-positive organisms.

Tube dilution testing: Microorganisms may be considered susceptible (likely to respond to minocycline therapy) if the minimum inhibitory concentration (M.I.C.) is not more than 4.0 mcg./ml. Microorganisms may be considered intermediate (harboring partial resistance) if the M.I.C. is 4.0 to 12.5 mcg./ml. and resistant (not likely to respond to minocycline therapy) if the M.I.C. is greater than 12.5 mcg./ml.

Susceptibility plate testing: If the Kirby-Bauer method of susceptibility testing (using a 30 mcg. tetracycline disc) gives a zone of 18 mm. or greater, the bacterial strain is considered to be susceptible to any tetracycline. Minocycline shows moderate *in vitro* activity against certain strains of staphylococci which have been found resistant to other tetracyclines. For such strains minocycline susceptibility powder may be used for additional susceptibility testing.

INDICATIONS. MINOCIN *minocycline HCl* is indicated in infections caused by the following microorganisms:

Rickettsiae: (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, tick fevers.)

Mycoplasma pneumoniae (PPLO, Eaton agent). Agents of psittacosis and ornithosis. Agents of lymphogranuloma venereum and granuloma inguinale. The spirochetal agent of relapsing fever (*Borrelia recurrentis*). The following gram-negative micro-organisms: *Hemophilus ducreyi* (chancroid), *Pasteurella pestis* and *Pasteurella tularensis*, *Bartonella bacilliformis*, *Bacteroides* species, *Vibrio comma* and *Vibrio fetus*, *Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of micro-organisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

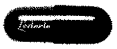
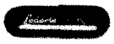
MINOCIN *minocycline HCl* is indicated for treatment of infections caused by the following gram-negative micro-organisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli, *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*), *Shigella* species, *Mima* species and *Herellea* species, *Haemophilus influenzae* (respiratory infections), *Klebsiella* species (respiratory and urinary infections).

MINOCIN is indicated for treatment of infections caused by the following gram-positive micro-organisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Streptococcus species: Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper-respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

FORM	ADULT DOSAGE (GENERAL)	PEDIATRIC DOSAGE (GENERAL)	HOW SUPPLIED
MINOCIN I.V. 100 mg/Vial	200 mg initially, 100 mg q. 12 h.	4 mg/kg initially, 2 mg/kg q. 12 h.	1 Vial 100 mg Box of 100 Vials
MINOCIN Capsules 100 mg 	200 mg initially, 100 mg q. 12 h.	4 mg/kg initially, 2 mg/kg q. 12 h.	Bottles of 50's and 100's; Unit dose 10 x 10's.
MINOCIN Capsules 50 mg 	100 mg or 200 mg initially, 50 mg q.i.d.	4 mg/kg initially, 2 mg/kg q. 12 h.	Bottles of 100's
MINOCIN Syrup 50 mg/5 cc	2 teaspoonfuls (100 mg) initially, 1 teaspoonful (50 mg) q.i.d.	4 mg/kg initially, 2 mg/kg q. 12 h.	2-fluidounce Bottles

Diplococcus pneumoniae.
Staphylococcus aureus, skin and soft tissue infections. Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:

Neisseria gonorrhoeae, *Treponema pallidum* and *Treponema pertenue* (syphilis and yaws), *Listeria monocytogenes*, *Clostridium* species, *Bacillus anthracis*, *Fusobacterium fusiforme* (Vincent's infection), *Actinomyces* species.

In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.

MINOCIN is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral tetracyclines or with a combination of oral and topical agents.

Oral only: In severe acne, the tetracyclines may be useful adjunctive therapy. Minocycline is indicated in the treatment of asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

In order to preserve the usefulness of MINOCIN *minocycline HCl* in the treatment of asymptomatic meningococcal carriers, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the drug be reserved for situations in which the risk of meningococcal meningitis is high.

Minocycline is not indicated for the treatment of meningococcal infection.

CONTRAINDICATIONS. This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS. In the presence of renal dysfunction, particularly in pregnancy, intravenous tetracycline therapy in daily doses exceeding 2 grams has been associated with deaths through liver failure.

When the need for intensive treatment outweighs its potential dangers (mostly during pregnancy or in individuals with known or suspected renal or liver impairment), it is advisable to perform renal and liver function tests before and during therapy. Also tetracycline serum concentrations should be followed.

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable. This hazard is of particular importance in the parenteral administration of tetracyclines to pregnant or post-partum patients with pyelonephritis. When used under these circumstances, the blood level should not exceed 15 micrograms/ml. and liver function tests should be made at frequent intervals. Other potentially hepatotoxic drugs should not be prescribed concomitantly.

The use of tetracyclines during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracyclines, therefore, should not be used in this age group unless other drugs are not likely to be effective or are contraindicated.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. Studies to date indicate that photosensitivity does not occur with MINOCIN *minocycline HCl*.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis.

CNS side effects including lightheadedness, dizziness or vertigo have been reported. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and always disappear rapidly when the drug is discontinued.

Usage in Pregnancy. (See above "Warnings" about use during tooth development.)

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in newborns, infants, and children. (See above "Warnings" about use during tooth development.)

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg./kg. every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

PRECAUTIONS. As with other antibiotics preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

All infections due to Group A beta-hemolytic streptococci should be treated for at least 10 days.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

ADVERSE REACTIONS. Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.

These reactions have been caused by both the oral and parenteral administration of tetracyclines. Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See "Warnings.") Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See "Warnings.") Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus. Bulging fontanels have been reported in young infants following full therapeutic dosage. This sign disappeared rapidly when the drug was discontinued. Blood: Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. CNS: (See "Warnings.") When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION: ORAL. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided.

Concomitant therapy: Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given to patients taking oral tetracycline.

Studies to date have indicated that the absorption of MINOCIN is not notably influenced by foods and dairy products.

In patients with renal impairment: (See "Warnings.") Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

In the treatment of streptococcal infections, a therapeutic dose of tetracycline should be administered for at least 10 days.

ADULTS: The usual dosage of MINOCIN *minocycline HCl* is 200 mg. initially followed by 100 mg. every 12 hours. Alternatively if more frequent doses are preferred, two or four 50 mg. capsules may be given initially followed by one 50 mg. capsule four times daily.

CHILDREN: The usual dosage of MINOCIN *minocycline HCl* is 4 mg./Kg. initially followed by 2 mg./Kg. every 12 hours.

For treatment of syphilis, the usual dosage of MINOCIN should be administered over a period of 10-15 days. Close followup, including laboratory tests, is recommended.

Gonorrhea patients sensitive to penicillin may be treated with MINOCIN, administered as 200 mg. initially followed by 100 mg. every twelve hours for a minimum of 4 days, with post-therapy cultures within 2-3 days.

In the treatment of meningococcal carrier state recommended dose is 100 mg. every 12 hours for five days.

DOSAGE AND ADMINISTRATION: INTRAVENOUS. Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

ADULTS: Usual adult dose: 200 mg. followed by 100 mg. every 12 hours and should not exceed 400 mg. in 24 hours. The drug should be initially dissolved and then further diluted to 500-1,000 cc. with either Sodium Chloride Injection USP, Dextrose Injection USP, Dextrose and Sodium Chloride Injection USP, Ringer's Injection USP, or Lactated Ringer's Injection USP but not in other solution containing calcium (a precipitate may form).

The reconstituted solutions are stable at room temperature for 24 hours without significant loss of potency. Any unused portions must be discarded after that period. The final dilution for administration should be administered immediately.

CHILDREN: Usual pediatric dose: 4 mg./kg. followed by 2 mg./kg. every 12 hours.

In patients with renal impairment: (See "Warnings.")

Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

HOW SUPPLIED. Capsules—Minocycline Hydrochloride equivalent to 100 mg. Minocycline. Hardshell purple and orange. Bottles of 50 and 100. Unit Dose 10 x 10's. Product No. 5301.

Minocycline Hydrochloride equivalent to 50 mg. Minocycline. Hardshell orange. Bottles of 100 and Unit Dose 10 x 10's. Product No. 5300.

Syrup—Minocycline Hydrochloride equivalent to 50 mg. Minocycline per teaspoonful (5 cc.). Preserved with propylparaben 0.10% and butylparaben 0.06% with Alcohol USP 5% v/v. Custard-flavored in bottles of 2 fl. oz. Product No. 5313.

Intravenous—100 mg. vials of sterile cryodesiccated powder. Product No. 5305. (Combined 5/73)

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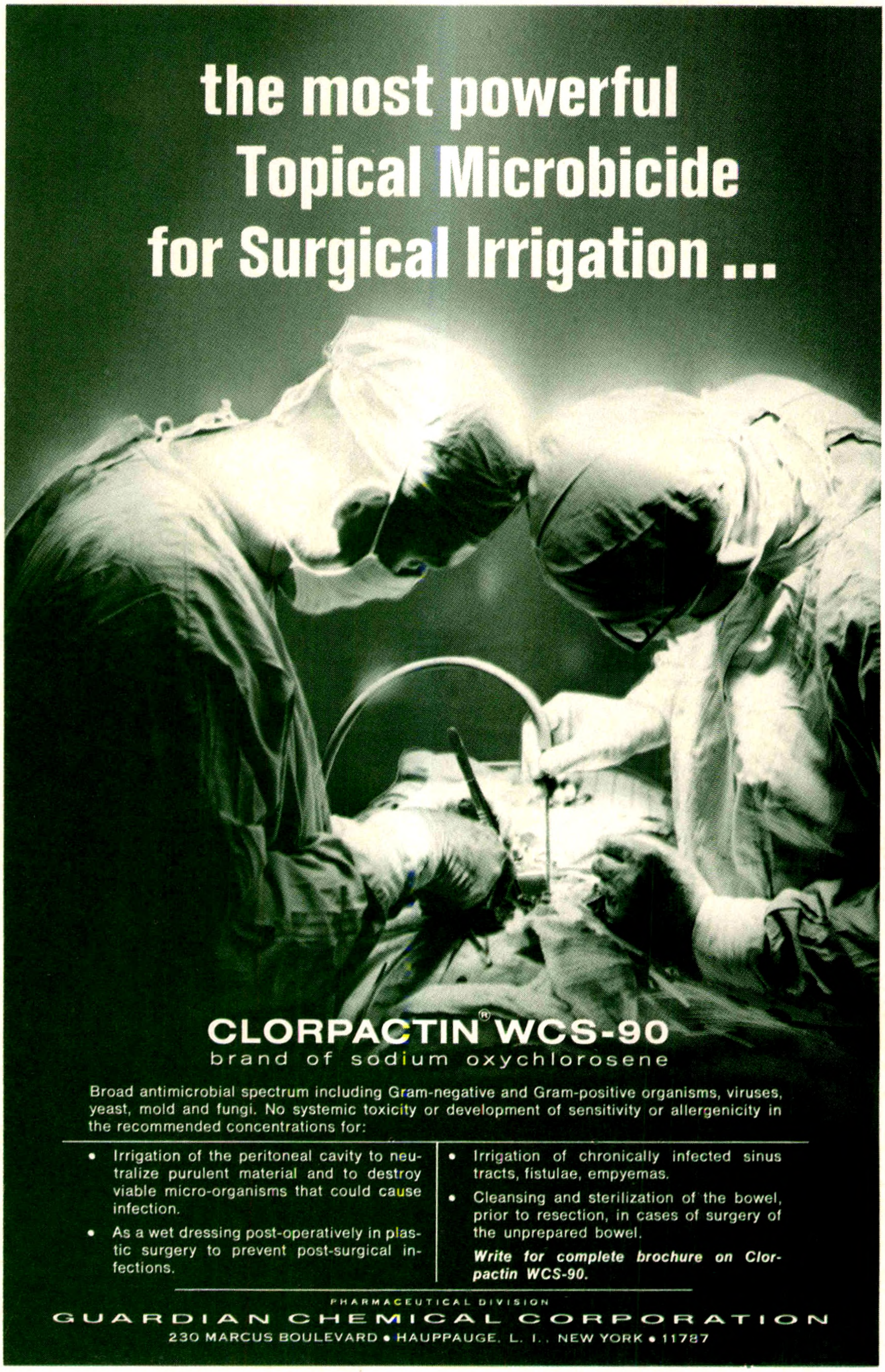

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Evaluation of Current Operations for the Prevention of Gastroesophageal Reflux

LTC TOM R. DEMEESTER, MC, LTC LAWRENCE F. JOHNSON, MC
COL. (RET.) ALFRED H. KENT, MC

From the Departments of Surgery and Medicine,
Tripler Army Medical Center,
Honolulu, Hawaii 96819

A prospective randomized study was done on 45 patients to evaluate the effectiveness of the Hill, Nissen or Belsey anti-reflux procedure. All patients had symptoms of GE reflux unresponsive to medical therapy, a + standard acid reflux test (SART), and esophagitis (38/45) or + Burnstein test (7/45). Esophageal symptomatic, radiographic, manometric and pH (SART and 24-hr monitoring) evaluation was done pre- and 154 days (ave.) postsurgery. All procedures improved the symptoms of pyrosis. The best improvement was seen after the Nissen repair. All procedures increased the distal esophageal sphincter (DES) pressures over preoperative levels. The Nissen and Belsey increased it more than the Hill. Sphincter length and dynamics remained unchanged. The Nissen procedure placed more of the manometric sphincter below the respiratory inversion point in the positive pressure environment of the abdomen. The esophageal length was increased by the Nissen and Hill repairs. This was thought to account for the high incidence of temporary postsurgery dysphagia following the Nissen and Hill repairs and the lower incidence following the Belsey repair. Reflux was most effectively prevented by the Nissen repair, as shown by the SART and the 24-hr esophageal pH monitoring, a sensitive measurement of frequency and duration of reflux. The average length of hospital stay was 20 days for Belsey and 12 days for both Nissen and Hill procedure. Postsurgery complications were more common following the thoracic than the abdominal approach. Ability to vomit post-repair was greatest with the Hill and least with the Belsey and Nissen repair. All procedures temporarily increased amount of flatus. It is concluded that the Nissen repair best controls reflux and its symptoms by providing the greatest increase in DES pressure and placing more of the sphincter in the positive abdominal environment. This is accomplished with the lowest morbidity but at the expense of temporary postoperative dysphagia and a 50% chance of being unable to vomit after the repair.

Surgeons have long been interested in the problem of hiatus hernia but not until the contribution of Allison[2] was the symptomatology of hiatus hernia linked to the occurrence of gastroesophageal reflux. This contribution directed surgeons' attention to the improvement of the function of the lower esophageal sphincter rather than simple reduction of the hernia by closure of the crura. The Allison repair was the first procedure to emphasize the replacement of the gastroesophageal junction into its normal intra-abdominal position in hopes of improving its function. Recognition of the high incidence of symptomatic and anatomic recurrences after the Allison repair[3,23] led to the development of procedures designed to place and anchor the lower esophagus in the intra-abdominal position in a more effective manner. A posterior gastropexy in which the phrenoesophageal membrane and the cardioesophageal junction are anchored to the median arcuate ligament of the aortic hiatus has been applied extensively by Hill.[11] More recently, two additional operations, the Belsey Mark IV[18] and the Nissen fundoplication,[16] have been introduced and were designed to reinforce the lower esophageal sphincter with a cuff of stomach as well as reestablishing an intra-abdominal segment of esophagus. The attractive features and promising clinical results from these new operative procedures have renewed interest in the surgical therapy of gastroesophageal reflux. However, considerable controversy exists over which of these new surgical repairs most effectively restore cardioesophageal competence. Recently, new tests of esophageal function have become available to evaluate the gastroesophageal

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Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

Reprint requests: LTC Tom R. DeMeester, MC, Department of Surgery, Box 272, Tripler Army Medical Center, Honolulu, Hawaii 96819.

sphincter and acid reflux.[12,14,22] To a limited extent these tests have been used to objectively evaluate the various surgical procedures.[10,19] We have undertaken a prospective randomized study to evaluate the comparative ability of the Hill, Belsey Mark IV and the Nissen procedure to restore cardioesophageal competence and prevent gastroesophageal reflux.

Method

The study was designed to be prospective on 45 patients who were randomized into three surgical treatment groups. Fifteen patients had the operation described by Hill, which is basically a posterior esophagogastropexy performed transabdominally by suturing the phrenoesophageal membrane and cardioesophageal junction to the median arcuate ligament of the aortic hiatus. This procedure incorporates a small plication of the lesser curvature of the stomach around the distal esophagus so as to narrow the esophageal gastric junction. Fifteen patients had the Mark IV operation described by Belsey. This is a transthoracic procedure which creates a 4 cm segment of intra-abdominal esophagus and buttresses it by a 270° gastric fundic wrap. Fifteen patients had the operation described by Nissen. This is a gastric fundoplication which is performed transabdominally in which the gastric fundus is wrapped 360° around the distal 4 cm of the esophagus to maintain it within the abdomen and buttress it at the same time. Both the Hill and Nissen repairs were performed over a 30 Fr. gastric tube. The 360° gastric fundic wrap in the Nissen operation was constructed so as to just allow the surgeon's index finger to pass through the center of the wrap adjacent to the incorporated distal esophagus. The Belsey repair was performed over a standard nasogastric tube. In all procedures, the right and left crura were approximated to a degree so as to allow the free insertion of the distal phalanx of the surgeon's index finger through the reconstructed esophageal hiatus. The choice of the surgical repair to be done on a study patient was made purely on a randomized basis by drawing a slip from a hat. The chosen Hill, Belsey Mark IV or Nissen procedure was performed by one of the chief surgical residents with one of the surgical staff as the first assistant. This was done so that the results obtained were more a reflection of the surgical repair than the skill of any one particular surgeon. The results of the study would therefore be reproducible by any surgeon endowed with average technical skill.

To be included in the study population, a patient had to meet four criteria: 1) He must possess symptoms of gastroesophageal reflux which have failed to respond to standard medical therapy supervised by one of our gastroenterologists. 2) He must demonstrate objective evidence of abnormal reflux of acid into the esophagus indicated by a positive standard acid reflux test. 3) He must show objective evidence of esophagitis (present in 38 of the 45 patients) or have a positive Bernstein test (present in 7 of the 45 patients). 4) He must be free of associated diseases such as cholelithiasis or peptic ulcer.

Each patient had extensive preoperative evaluation with a battery of esophageal function studies. At an average of 154 days following the surgical repair, these studies were repeated and a subjective postsurgical evaluation obtained. The range of time between the surgical repair and the postsurgical evaluation was 30–696 days. The most common interval was 80–130 days (28 patients). Eight patients received their followup between 30 and 80 days and nine other patients had two postsurgical evaluations, one between 30 and 127 days and the second between 283 and 696 days postrepair. For the purpose of this report the results of the second study were used. The paired T-test was used for satistical comparison between the pre- and postoperative data obtained from each patient who had the same surgical procedure. The three surgical procedures were compared using Duncan's new multiple range test for statistical comparison.[20] The studies performed at the pre- and postsurgical evaluation were as follows:

Clinical Score

Each patient was graded on a scale of 0 to 3 for each of the symptoms of heartburn, regurgitation and dysphagia. The grading was done prior to any objective studies using a reflux questionnaire completed by one of the authors during an interview with the patient. The highest obtainable score was nine and would represent a patient with heartburn that interfered with daily activities, episodes of pulmonary aspiration secondary to regurgitation, and dysphagia requiring a hospital admission for relief of meat impaction. A similar clinical scoring was performed at the postsurgical evaluation, and each patient, without knowledge of the type of repair he had had, was evaluated as to the duration of postrepair dysphagia (i.e., any subjective discomfort during swallowing), the need for postsurgical dilatations, the ability to vomit, the ability to belch, the presence of increased flatus, the presence of diarrhea, and the presence of periodic episodes of abdominal distention.

Radiographic Studies

Each patient was evaluated radiologically for a demonstrable hiatus hernia, evidences of gastroesophageal reflux, and the presence of an associated gastric or duodenal lesion. The study was done by an interested, skilled radiologist who employed the head-down Valsalva maneuver to demonstrate a hiatus hernia and to provoke reflux of gastric contents into the esophagus. A cholecystogram was done on all patients to exclude the presence of gallbladder disease. At the time of the postsurgical evaluation, the radiographic study was repeated to confirm the reduction or recurrence of the hernia, to determine the presence or absence of gastroesophageal reflux, and to measure the length of esophagus placed below the diaphragm by each surgical repair.

Endoscopy

Esophagoscopy and biopsy of the distal esophagus was performed in all patients preoperatively to determine grossly and histologically the presence of esophagitis. At the time of esophagoscopy, gastroscopy and duodenoscopy were also performed to further assure the absence of an associated gastric or duodenal lesion. Esophagoscopy was not performed at the postsurgical evaluation on asymptomatic patients.

Esophageal Manometry

Manometric evaluation was performed according to the technique of Wynant[22] using a single catheter assembly consisting of three fluid-filled, perfused polyethylene tubes bonded together with three 2 mm lateral openings placed 5 cm apart at its distal end. The catheter was passed into the empty stomach like a nasogastric tube and withdrawn in 1 cm increments from the stomach into the esophagus and up to the cricopharyngeus muscle. Using this technique, the location and resting pressure of the distal esophageal sphincter (DES), the location of respiratory inversion point, the length of the esophagus from the bottom of the DES to the bottom of the cricopharyngeal high pressure zone, and the presence of abnormal motility represented by repetitive, spontaneous, simultaneous, and powerful broad base esophageal contractions was obtained. DES pressure was measured as the difference in mm of Hg between the resting end-expiratory gastric pressure and the sphincter pressure at the respiratory inversion point. The abdominal compression was performed by hand causing an increase in the intragastric pressure between 10 and 20 mm Hg while simultaneously recording pressures from the stomach, DES and esophagus.

Acid Clearance Test

This test was performed as described by Booth and associates[4] by instilling 15 cc of 0.1 normal HCL into the esophagus 15 cm above the DES. The number of effective swallows recorded on the motility record to return the intraesophageal pH to 5 was determined. Greater than 10 swallows was considered abnormal.

Standard Acid Reflux Test

Each patient had a standard acid reflux test performed pre- and postoperatively in which 300 cc of 0.1 normal HCL was inserted through the motility catheter to provide a standard volume and pH within the stomach. The motility catheter was then withdrawn into the esophagus so that the pH electrode located at its tip lay 5 cm above the DES. The pH of the esophagus was then monitored while the patient rested quietly in the supine position and then performed four maneuvers; deep breathing, Valsalva, Mueller (inspiration against a closed clottis) and cough. These maneuvers were repeated in the right and left lateral decubitus position and with the head down 20°, giving 16 possibilities for gastroesophageal reflux to occur. A decrease in esophageal pH to less than 4 was considered evidence of reflux.[14] At the beginning of a test, prior to placing the patient in the supine position, the distal esophagus had to have a pH greater than 4. In several patients this necessitated standing erect and swallowing repeatedly in order to clear the esophagus of acid. Patients who failed to clear the esophagus in the erect position after 20 effective swallows monitored on the motility tracing were considered to be abnormal in all positions and maneuvers and scored as 16. Results obtained with this standard acid reflux test have been reviewed in 91 normal volunteers.[19] Two or less reflux episodes out of 16 trials constitutes a normal finding.

24-Hour Esophageal pH Monitoring

Thirty-four of the 45 patients gave permission for a 24-hour pH monitoring of their distal esophagus at their pre- and postsurgical evaluation. Seven of the 45 patients volunteered only for postsurgical monitoring. Four of the 45 patients did not grant permission for either. The technique of the 24-hour pH monitoring of the distal esophagus has been recently reported by the authors.[12] It consists of positioning a pH electrode 5 cm above the distal esophageal sphincter previously located by infusion manometry and a reference lead on the forearm using a technique that assures good electrical contact. Both the pH probe and reference lead are connected via a pH meter to a strip chart recorder running at 6 inches per hour for 24 hours. A normal diet is served during this period, unique only in the absence of food and beverages having a pH value of less than 5. All individuals were given a pencil to mark on the strip chart recorder any subjectie reflux symptoms that occurred as well as their body position, upright or supine. Reflux was defined whenever the pH in the esophagus dropped to less than 4. From the 24-hour record, the per cent time the pH was less than 4 in the distal esophagus could be determined for the total 24-hour period and for the time spent in the upright and supine positions. In addition, the total number of reflux episodes, the number of episodes greater than 5 minutes, and the length of the longest reflux episode can be obtained from the tracing.

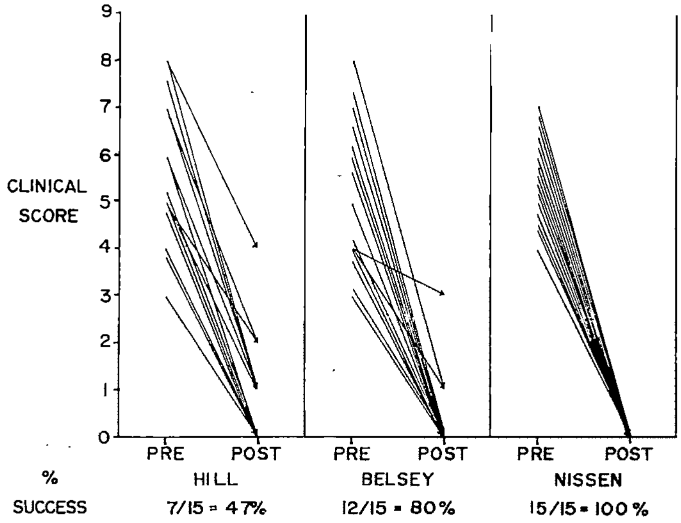


FIG. 1. Pre- and postrepair changes in the clinical score. Each patient served as his own control. See text for explanation of score. % success = the percent of patients returned to normal (clinical score of 0) postrepair.

This gave six components from the 24-hour record in which each patient was measured. Each patient was given a numerical 24-hour pH score, as a means of comparing the overall results of the 24-hour pH monitoring test. The contribution of each component to the 24-hour pH score was appropriately weighed for its sensitivity for determining the presence of reflux. Normal values for each component and the 24-hour pH score were two standard deviations above the mean values obtained from 15 asymptomatic volunteer subjects.

Results

Clinical Score

Figure 1 shows the effect of each repair on the preoperative clinical score. Only the Nissen procedure resulted in 100% improvement in the clinical score postsurgery. Of the 15 patients with a postsurgical score of 0, none had objective evidence of recurrence of gastroesophageal reflux.

All of the patients with a Hill repair who had a postsurgical clinical score of greater than 1 also had objective evidence for the recurrence of reflux on pH testing. Only one of the five patients with a postsurgical score of 1, and one of the seven patients with a postsurgical score of 0, had objective evidence of recurrence of reflux.

Of the three patients with the Belsey repair who had a postsurgical score greater than 0, two had objective evidence of recurrence of reflux on pH testing. Of the 12 patients who had a postoperative score of 0, four had objective evidence for recurrence of reflux on pH testing.

Radiographic Studies

Table 1 shows the results of the radiographic studies. Thirty-nine of the 45 patients or 86% had a hiatus hernia demonstrated preoperatively. Only 51% of the patients demonstrated the presence of radiographic reflux. Postoperatively, none of the patients with a Nissen repair and only one of the patients with a Hill repair had a recurrence of his hernia and this was associated with objective evidence of recurrence of reflux on pH testing. Similarly, three of the patients with a Belsey repair had a postoperative hiatus hernia demonstrated and these were also associated with objective evidence of the recurrence of reflux on pH testing. Three patients with the Hill repair and four patients with the Belsey repair did not show recurrence of their hiatal hernia but did have objective evidence on 24-hr pH testing for the recurrence of reflux. Only one patient demonstrated radiographic evidence of gastroesophageal reflux postsurgically. He also had objective evidence on pH testing of gastroesophageal reflux. All repairs, except when there was a recurrence of the hernia, increased the amount of intra-abdominal esophagus as measured radiographically, but the presence of an adequate intra-abdominal esophagus was not a reliable indication for the absence of reflux. Seven of the 45 patients who had objective evidence for recurrence of reflux on pH testing did not have a recurrent hiatal hernia and did show an adequate intra-abdominal esophagus measuring 2–4.5 cm.

TABLE 1. *Radiographic Findings*

		Radiographic Hiatus Hernia		Radiographic Reflux		Length of Abdominal Esophagus (Post repair in cm)	
Repair	No. of Patients	Pre	Post	Pre	Post	All Patients without Recurrent Hernias	Patients with Negative 24-hr pH Reflux Test
Hill	15	12	1	11	0	3.1 ± 0.9**	3.0 ± 0.9**
Belsey	15	14	3	6	1	3.7 ± 0.7	3.9 ± 0.7*
Nissen	15	13	0	6	0	4.1 ± 1.4*	4.1 ± 14*
Total	45	39 (86%)	4	23 (51%)	1		

* Statistically greater than double starred (**) values — $p < .05$

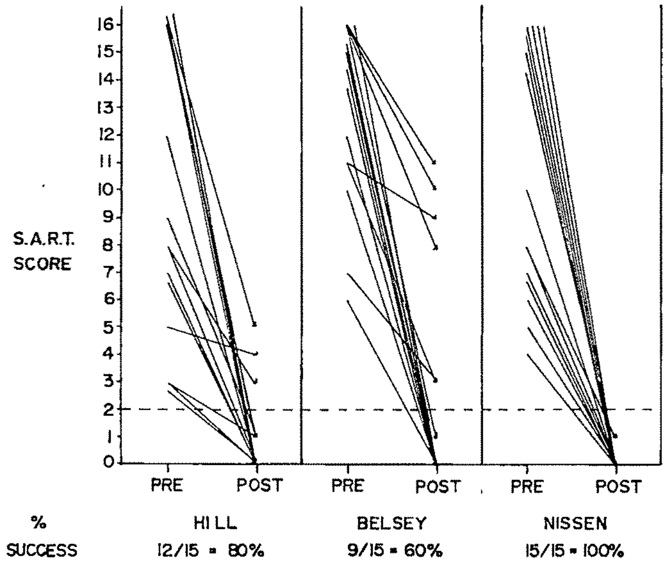


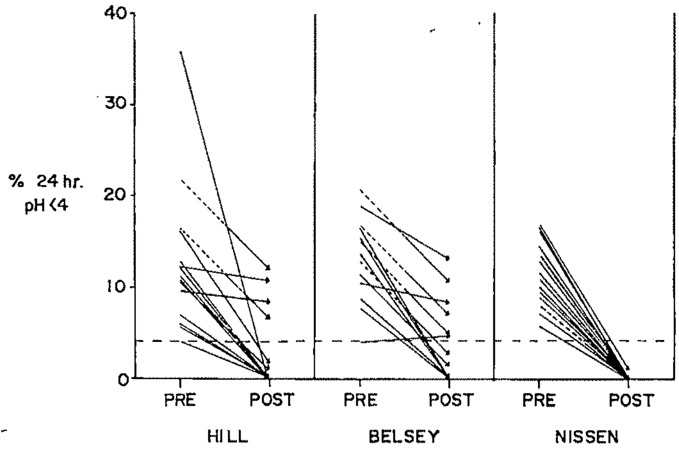
FIG. 2. Pre- and postrepair changes in standard acid reflux test (S.A.R.T.). Each patient served as his own control. See test for explanation of score. % success = the percent of patients returned to normal (below the broken line) postrepair.

pH Reflux Test

The results of the standard acid reflux test are shown in Fig. 2. All patients had an abnormal standard acid reflux test preoperatively. The Nissen repair returned all the patients to normal postsurgically. The Hill and Belsey repairs were successful in returning only 80% and 60% of the patients to normal, respectively.

Esophageal pH Monitoring

Figure 3 shows the effect of each repair on the 24-hour pH monitoring of the distal esophagus. In each component of the 24-hour pH record (Figs. 3a–f) the Nissen procedure returned all the postsurgical patients to a normal level. Both the Hill and Belsey repairs consistently failed in this regard, but quantitatively both repairs decreased the amount of reflux over its preoperative level. With few exceptions, those patients who failed to return to normal in one component were the same who failed to return to normal in the other components. There was little difference between the ability of the Hill or Belsey repairs to protect from reflux in either the supine or upright positions. The longest reflux episodes recorded during the monitoring period were in those patients who had a Belsey repair (Fig. 3f) and shows the failure of these patients to clear their distal esophagus of acid after a reflux episode has occurred. The Nissen repair gave complete protection against



FIGS. 3a–g. Pre- and postrepair changes in 24-hour monitoring of the distal esophagus. Each patient served as his own control. % success = the percent of patients returned to normal (below the broken line) postrepair. Half broken arrows = postrepair values in which there was no corresponding preoperative measurement. FIG. 3a. % time pH was <4 for the 24 hours.

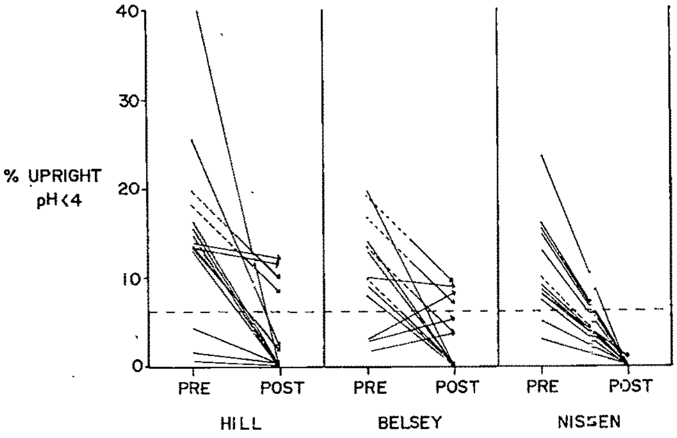


FIG. 3b. % time pH was <4 for the time spent in the upright position (av. 900 min).

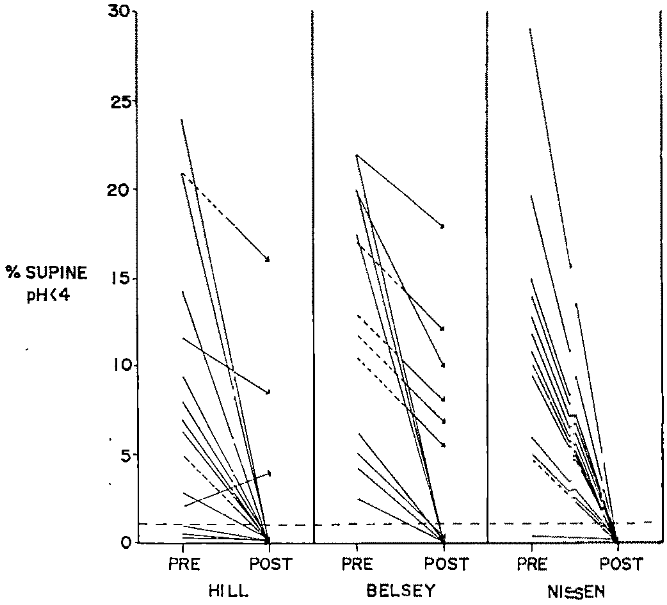


FIG. 3c. % time pH was <4 for the time spent in the supine position (av. 540 min).

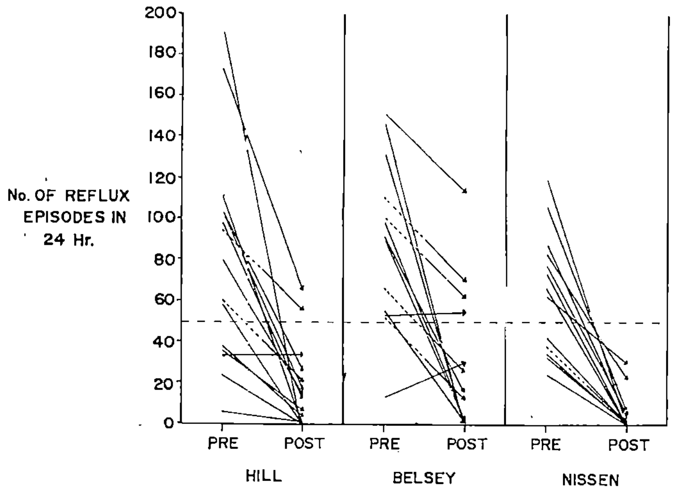


FIG. 3d.

gastroesophageal reflux in both the supine and upright positions. It also reduced the number of reflux episodes to normal and did not interfere with the ability of the esophagus to clear itself of acid after a reflux episode. Figure 3g shows a comparison between each repair based on the 24-hour pH score, a numerical valve used to express the overall result of the 24-hour pH monitoring test. Using this sensitive quantitative index for the occurrence of reflux, the Belsey and Hill repairs were successful in returning only 46% and 73% of the patients to normal, respectively. One hundred percent of the patients receiving the Nissen repair were returned to normal.

Esophageal Manometry

Sphincter Pressure. All repairs significantly increase sphincter pressure over that of preoperative levels (Fig. 4). Those procedures incorporating a form of fundic wrap, that is, the Belsey and the Nissen repairs, increase the sphincter pressure significantly more than the Hill repair ($p < .01$ Nissen vs Hill and $p < .05$ Belsey vs Hill). Although the Nissen repair which incorporates a 360° wrap increased the sphincter pressure the greatest, it was not statistically different from the increase in pressure produced by the Belsey repair which incorporates a 270° gastric fundic wrap. Failure to increase the sphincter pressure in a patient postoperatively was not related to the presence of objectively measured gastroesophageal reflux on pH studies.

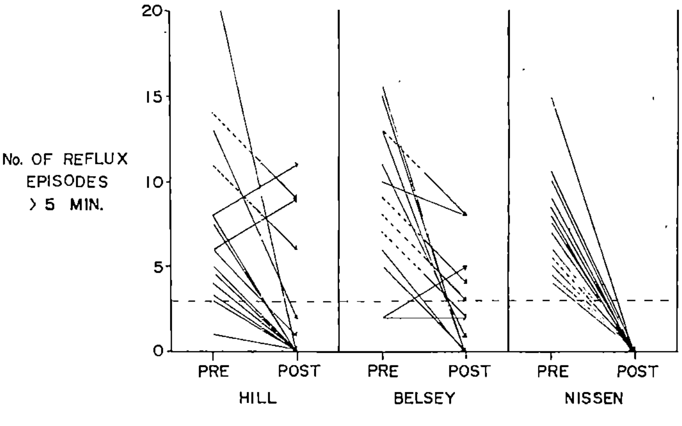


FIG. 3e.

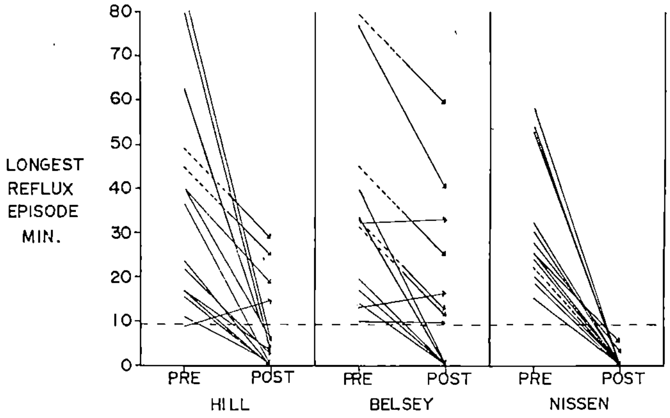


FIG. 3f.

Sphincter Characteristics. Sphincter dynamics, that is, relaxation on swallowing followed by a contracture, based on a qualitative evaluation remain unchanged after each of the repairs. The length of the sphincter was significantly increased over its preoperative length by 0.7 cm following the Hill repair; indicating a considerable stretch was applied to the sphincter area by performing the posterior abdominal gastroesophagealpexy (Fig. 5). This was not so for the Belsey or the Nissen

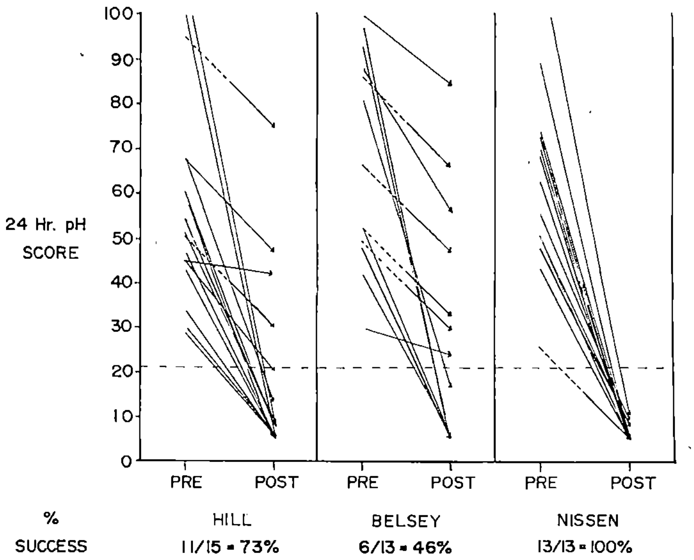


FIG. 3g. Composite score for the 24 hours based on the measurements of the 6 preceding components. See text for explanation.

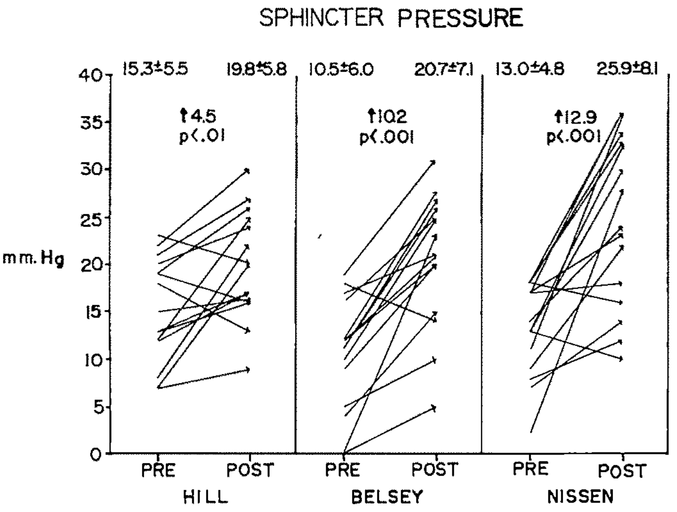


FIG. 4. Pre- and postrepair changes in DES pressure. Each patient served as his own control.

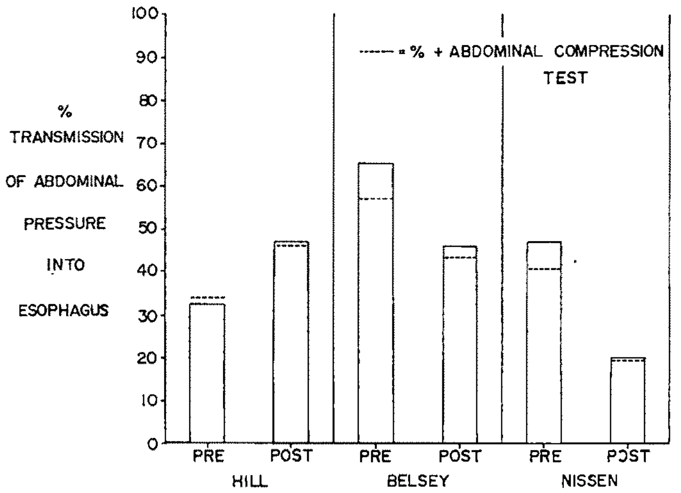


FIG. 6. Pre- and postrepair changes in the abdominal compression test scored as % positive and % transmission of abdominal pressure into esophagus. Each group served as its own control.

repair. The length of sphincter below the respiratory inversion point, that is, in the area of the positive pressure environment of the abdomen, was increased by all three procedures over the preoperative values. This was significant, however, only for the Nissen (Fig. 5). If one disregards those patients who had objective evidence of recurrence of reflux on pH study from the 15 patients with the Belsey repair, the amount of the sphincter placed below the respiratory inversion point over the preoperative levels becomes statistically significant ($p < .02$). This was not so for the Hill repair.

Abdominal Compression Test. The resistance of the sphincter to the transmission of an increase in gastric pressure into the esophagus is shown in Fig. 6. The Hill repair did not improve the resistance of the sphincter to a rise in gastric pressure. The gastric fundic wrap procedures, however, decreased the amount of gastric pressure which was transmitted into the esophagus postsurgically over the preoperative controls. This decrease was greatest with the Nissen procedure which creates a 360° wrap as opposed to the 270° wrap of the Belsey. Only the changes after the Nissen repair bordered on statistical significance with a p value $< .1$ but $> .05$. If the abdominal compression test is recorded as a positive or a negative result based on the presence or absence of any rise in the esophageal pressure secondary to an increase in gastric pressure, a similar comparison resulted and is represented by the dotted lines on Fig. 6. Again, however, the changes were not significant.

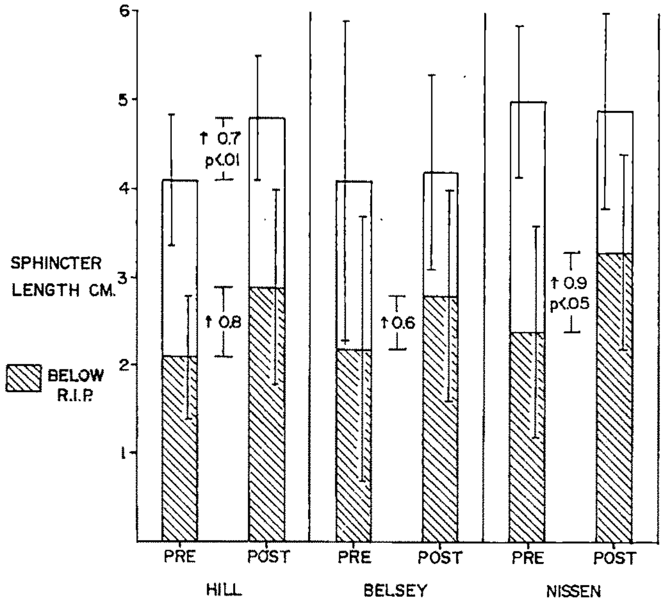


FIG. 5. Pre- and postrepair changes in DES overall length and the amount below the respiratory inversion point (R.I.P.) Each group served as its own control.

Esophageal Length. Both the Hill and the Nissen repair significantly increase the length of the esophagus as measured from the bottom of the cricopharyngeal high pressure zone to the bottom of the DES (Fig. 7). This was not so for the Belsey repair in which the distal esophagus is mobilized from its adjacent structures within the chest.

Esophageal Motility. Figure 8 shows the effect of the various procedures on esophageal motility. Each repair was performed on patients who had some evidence of motility disturbance preoperatively. On the postsurgical examination a change from abnormal motility to normal motility was seen following each repair. There was also a change from a normal preoperative motility to an abnormal postsurgical motility associated with each repair. A few patients remained abnormal pre- and postsurgery.

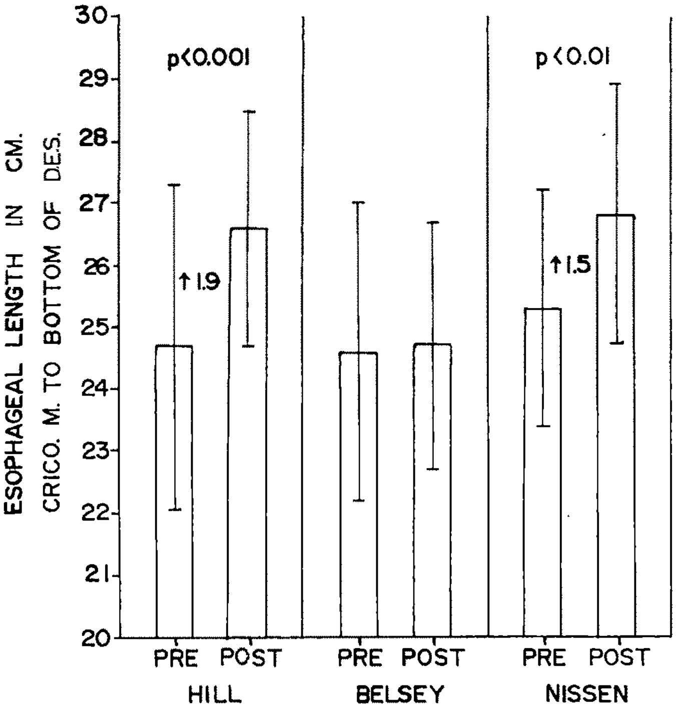


FIG. 7. Pre- and postrepair changes in esophageal length. Each group served as its own control.

Acid Clearance Test

Table 2 shows the effects of each procedure on the acid clearance test and indicates that most patients were abnormal preoperatively with about half of them becoming normal and half remaining unchanged after repair. There was no clear pattern on the effects of the three repairs on the acid clearance test.

Surgical Morbidity

Discounting the presence of a wound infection, there were three patients with complications out of the 15 patients who received the Hill repair. These complications were related to the technique of the repair. There were two patients who suffered a minor arterial injury to the celiac axis while anchoring the gastroesophageal junction to the median arcuate ligament. One patient developed decreased gastric motility with the formation of a gastric bezoar. Two of the 15 patients who received the Belsey repair had complications due to the thoracic approach and not the repair itself. One patient had a severe postoperative pneumonia and a second patient had a recurrent pleural effusion. Two of the 15 patients who received the Nissen repair had complications. One patient suffered an esophageal perforation while performing the repair. This, however, did not add to his postsurgical morbidity or interfere with the functional result of the repair. The second patient developed postoperative bowel obstruction secondary to adhesions. The average hospital stay for patients without complications was 10 days for the Hill repair, 13 days for the Belsey repair and 11 days for the Nissen repair.

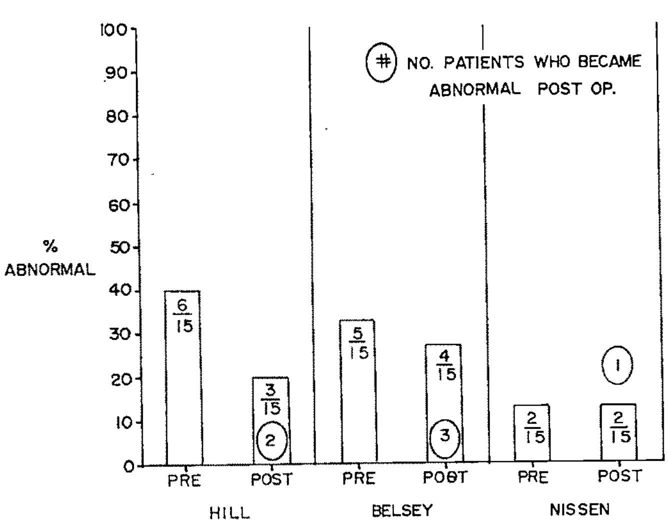


FIG. 8. Pre- and postrepair changes in esophageal motility.

Postsurgical Subjective Evaluation

From 46% to 60% of the patients had symptoms of preoperative dysphagia (Fig. 9). This was aggravated by the Hill and Nissen repairs and improved slightly by the Belsey repair during the immediate postoperative period. If a patient experienced dysphagia postsurgery, the duration of the dysphagia was the same regardless of the repair used. Postsurgical dilatations to relieve dysphagia were required in four patients, two with the Hill repair, one with the Belsey and Nissen repair. In all patients, dysphagia was absent six months following repair regardless of the procedure used.

Seventy per cent of the patients receiving the Hill procedure were able to vomit. This was true of only 50% and 45% of the patients with Belsey and Nissen repairs, respectively (Fig. 10). The ability to belch was about the same for each procedure with 85% to 93% of the patients reporting their ability to do so. All procedures caused an increase in the amount of flatus. This was temporary in duration and usually absent after six months. Both the Hill and Nissen procedures had a relatively high incidence of temporary postoperative diarrhea. This was not so for the Belsey procedure. There

TABLE 2. *Acid Clearance Test*

Test Results			No. of Patients	
Pre	Post	Hill	Belsey	Nissen
Normal	→ Normal	1	1	4
Abnormal	→ Abnormal	3	8	5
Abnormal	→ Normal	9	5	4
Normal	→ Abnormal	2	1	2
		15	15	15

was little difference between the various procedures as to periodic episodes of abdominal distention.

Long-term Followup Studies

Table 3 shows the changes in those patients who had two postsurgical studies. Each of the three procedures had three of these patients. One patient with a Hill and two patients with a Belsey repair had a late recurrence of acid reflux as measured by pH studies. None of the three patients with a Nissen repair had a late recurrence.

Discussion

The goal of surgical treatment for gastroesophageal reflux is restoration of cardioesophageal competence. The high rate of symptoms from persistent acid reflux after simple crural repair of the esophageal hiatus has led to the development of new operative techniques that incorporate maneuvers designed to place the lower esophageal sphincter in the intra-abdominal position where it is thought to function more effectively and to reinforce the lower esophageal sphincter by a cuff of gastric fundus which is wrapped around the intra-abdominal esophagus.

The operations which bear the names of Hill, Belsey and Nissen incorporate one or both of these maneuvers. Hill reported on 149 patients having his repair with no anatomic recurrences of the hernia and a 97% symptomatic improvement.[11] Skinner and Belsey[18] reported on 632 patients with the Belsey Mark IV repair and showed a 7% anatomic recurrence of the hernia and an 85% relief of acid reflux symptoms. A worldwide survey of the results of Nissen repair showed a 3% anatomic recurrence of the hernia and a 96% improvement in the symptoms of gastroesophageal reflux.[17]

Deficiencies common to these above reports are their retrospective nature, their lack of randomization of patients, and their lack of objective pre- and postoperative evaluation of reflux with pH studies. Basing the effectiveness of a procedure on the presence or absence of a radiographic recurrence of the anatomic hernia or radiographic evidence of gastroesophageal reflux is of questionable value. Many reports have shown that gastroesophageal reflux can occur in the absence of an anatomical hiatal hernia.[9] This is seen to occur particularly in patients who have had previous esophageal surgery. Therefore, the absence of an anatomical recurrence of the hiatal hernia is no guarantee that reflux is not occurring. The present study indicated that when reflux is objectively measured on the basis of pH studies using the 24-hour pH monitoring technique, recurrence of postrepair reflux was seen in 11 of the 41 patients (Fig. 3g). Seven of these patients did not show a recurrence of the anatomical hernia. However, those four patients who demonstrate recurrence of the anatomical hernia also had recurrence of gastroesophageal reflux on the basis of pH studies indicating that the recurrence of the anatomic hernia postrepair is associated with recurrence of reflux. The presence of gastroesophageal reflux demonstrated on fluoroscopy is also not a reliable means for evaluating the presence of reflux after surgical repair. All of the 45 patients in this study showed objective evidence of reflux on pH studies using the standard reflux test and the 24-hour pH monitoring but only 51% of them demonstrated radiographic reflux on fluoroscopy (Table 1). Similarly, symptoms are not a reliable guide to the presence of reflux as manifested by several patients in this study who had improved clinical scores postsurgery but showed objective evidence of gastroesophageal reflux on pH studies.

Currently, the best way to ascertain whether the goal of surgical treatment, that is, restoration of cardioesophageal competence, has been accomplished is the use of pH studies such as the standard acid reflux test or 24-hour pH monitoring of the esophagus. The standard acid reflux test primes the patient by placing hydro-

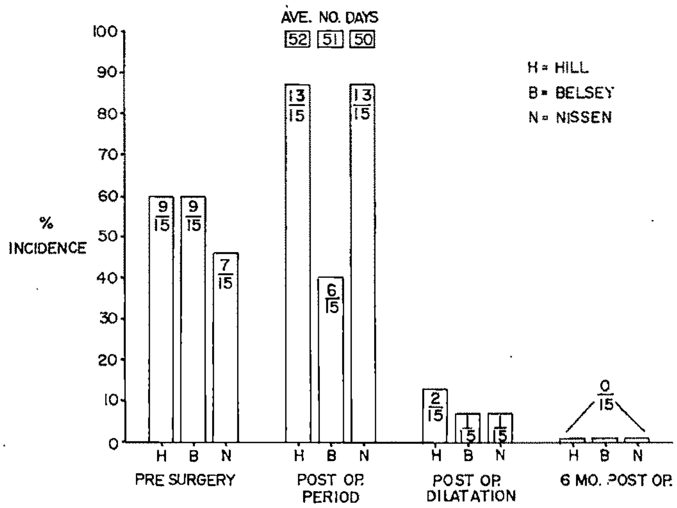


Fig. 9. The effect of each repair on the symptoms of dysphagia.

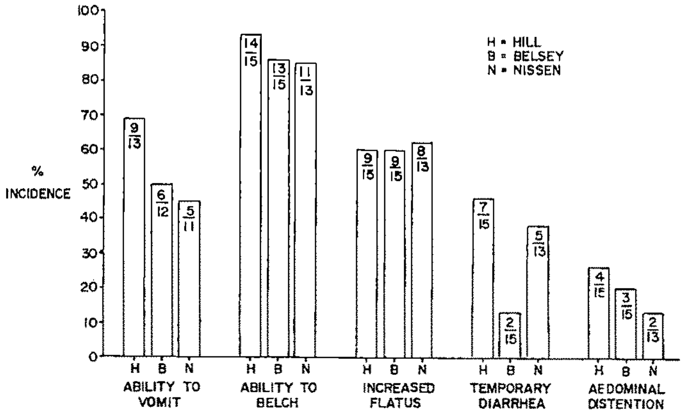


Fig. 10. The morbidity of each repair.

TABLE 3. *Long-term Followup Studies*

Procedure	Patient No.	Time in Days to Postop Study 1st Study	2nd Study	Reflux Test 1st Study	2nd Study
Hill	1	34	328	–	–
	2	53	283	–	+
	3	65	295	–	–
Belsey	1	35	696	–	–
	2	74	586	–	+
	3	65	515	–	+
Nissen	1	58	478	–	–
	2	74	439	–	–
	3	134	394	–	–

chloric acid within his stomach and attempts to induce reflux by having him perform maneuvers in different positions. Using this test, which weighs the chances in favor of producing reflux, the Nissen procedure gave 100% protection. This was not so for the Hill or Belsey (Fig. 2). The 24-hour pH monitoring of the distal esophagus is a less invasive technique and measures the amount of reflux that the patient generates on his own without being primed by the installation of acid into the stomach or the performance of unnatural maneuvers in an attempt to induce reflux. The 24-hour pH monitoring of the distal esophagus therefore quantitates gastroesophageal reflux in a near physiologic setting by measuring the frequency and duration of the esophageal mucosa's exposure to acid. This test has been shown capable of distinguishing between asymptomatic volunteers and patients with symptoms of gastroesophageal reflux by six components of the 24-hour record and a derived composite score.[12] Using this test preoperatively and after the various surgical repairs, only the Nissen gave complete protection against gastroesophageal reflux (Fig. 3g). Using this more sensitive technique of quantitating gastroesophageal reflux, the Belsey and Hill repairs gave less protection against reflux than that measured using the standard acid reflux test (Fig. 2 vs Fig. 3g). The 24-hour pH monitor test also affords an opportunity to evaluate cardioesophageal competence in the upright and supine positions, that is, when the patient has the aid of gravity in the upright position to prevent reflux and the encouragement to reflux by gravity in the supine position. In both of these positions the Nissen gave a complete protection against reflux and this was not seen following the Hill or Belsey repair (Fig. 3b, c). The 24-hour pH esophageal monitoring also affords an opportunity to quantitate the number of reflux episodes in a 24-hour period. We have recently shown that the number of reflux episodes which are 5 minutes or greater in duration are of greater consequence in producing esophagitis than those which are cleared more rapidly.[13] The Nissen repair does not cause an abnormal number of 5-minute or longer reflux episodes (Fig. 3e) and any physiological reflux that occurs is not hampered in its clearance from the esophagus. This was not so with the Belsey or Hill procedures. Of significance is the fact that the longest reflux episodes recorded during the 24-hour period of monitoring were from those patients receiving the Belsey repair (Fig. 3b). This was less so for those receiving the Hill repair, but no abnormally long reflux episode was recorded in any of the patients receiving the Nissen procedure. This would suggest that the mobilization of the distal esophagus during the transthoracic Belsey approach may interfere with clearing of the acid from the distal esophagus following an episode of reflux. When the results of the pH tests are critically evaluated, the Nissen repair more effectively obtains the goal of surgical treatment, this is, establishing gastroesophageal competence, than either the Hill or Belsey repair.

Although the results of these studies indicate that the Nissen repair best controls gastroesophageal reflux, it must be emphasized that they represent results obtained after an average of 154 days following the surgical repair. The ultimate answer will come when the state of these repairs is evaluated at five and ten years after the operative procedure. In those patients who had second postsurgical studies at a later date (Table 3), only those who received the Nissen repair have remained unchanged in the competency of their cardioesophageal junction. On the other hand, two of the three patients who received the Belsey repair and one of the three patients who received the Hill repair showed a late loss in cardioesophageal competence and the recurrence of gastroesophageal reflux. It is encouraging to see that the Nissen repair has remained unchanged. There is no guarantee that it will continue to remain so, but a good long-term result obviously depends on the absence of recurrence in the early postoperative period. It is hard to believe that an initial poor result in an operative repair will improve with time.

Both the Hill and Nissen repairs resulted in a similar incidence of postsurgical dysphagia. The Belsey repair was associated with markedly less dysphagia (Fig. 9). Of interest is the finding that both the Hill and Nissen repairs significantly increased the length of the esophagus from the bottom of the cricopharyngeus muscle to the bottom of the DES, whereas the Belsey repair did not (Fig. 7). This would strongly suggest that the degree of dysphagia postrepair was related to stretching the esophagus rather than too vigorous approximation of the crura. Using radiopaque markers on the esophagus, Dodds and associates[8] have shown that the magnitude and duration of all excursion of the esophagus during peristalsis was significantly greater for the distal end of the esophagus than the proximal area. Actual measurement showed that immediately after the onset of peristalsis there was a prominent oral movement of markers on the distal esophagus for a distance of 1 cm or more above their mean respiratory position as the esophagus shortened to dilate and engulf a passing bolus. It seems reasonable to suspect that the stretching of the esophagus secondary to the Hill and Nissen repairs limits the amount of oral extension of the distal esophagus during peristalsis, thus making it difficult for the esophagus to dilate and accept a bolus of food. This would give rise to the symptoms of dysphagia which these patients experience. After a period of time in which the tissues were able to accommodate to the new length, the symptoms of dysphagia should disappear. This was indeed the case in that all patients were free of dysphagia after six months. Indeed, in those patients who had the Hill or Nissen repair and who had a second postsurgical study at a later date, the esophagus had returned to its normal preoperative length. This was accomplished by lowering the bottom of the cricopharyngeus muscle indicating that the increase in length was made up in elongation of the hypopharynx.

Thirteen of 45 patients in this study or 28% had some evidence of motility disturbances as manifested by spontaneous, simultaneous and repetitive esophageal contractions on their preoperative motility study. In all but three of these patients the motility abnormality was absent on the postsurgical study suggesting that the etiology for the motility disturbance was the presence of gastroesophageal reflux (Fig. 8). It should be emphasized, however, that each repair was responsible for the change of a normal preoperative motility to an abnormal motility postrepair (Fig. 8). Based on this information, we do not feel that a motility disorder manifested by simultaneous, spontaneous and repetitive esophageal contractions and associated with reflux is a contraindication for surgery. Nor should it be used as has been advocated,[7] as an indication for a concomitant myotomy at the time of surgical repair, since the majority of these motility abnormalities will disappear once reflux is controlled. A small number of patients, however, will remain abnormal postrepair but it is difficult to determine which ones will do so. If a myotomy is added to the surgical repair for reflux in all those patients manifesting a motility abnormality, a significant risk will be added to several patients where it is not justified.

A decrease in the ability to vomit was seen after all repairs. This was most marked for the Nissen and Belsey procedures which incorporate a gastric fundic wrap in their construction. The ability to belch after each repair was about the same. An increase in the amount of flatus was noted to the same degree in patients regardless of the procedure used to restore cardioesophageal competence. It is our feeling that this increase in flatus is secondary to the marked aerophagia that a significant number of these people manifest. When this habit is broken postoperatively, the degree of flatus experienced by the patient decreases rapidly. Both the Nissen and the Hill procedures have a relatively high incidence of diarrhea postrepair. This was not so for the Belsey repair. A probable explanation may be that the vaguses were more apt to be injured during abdominal approach, giving rise to a period of vagal paresis and a postvagotomy diarrhea syndrome. In each incidence the diarrhea was temporary and bowel habits returned to normal. The problem of abdominal bloating following the Nissen repair has occurred only in two of the 15 patients and has not been seen to the incidence reported by others.[23] This is probably due to constructing the gastric fundic wrap over a 30 Fr. gastric tube and limiting it to the distal 4 cm of the esophagus. A longer or tighter fundic wrap may make the sphincter super competent and severely impair the patient's ability to eructate, giving rise to the gas bloat syndrome.

The question arises as to why the Nissen repair is superior to the Hill and Belsey repairs in preventing gastroesophageal reflux. To answer this question one must consider two principles that are seemingly important in gastroesophageal reflux. First, there is strong evidence that the sphincter pressure recorded by continuous perfusion is less than normal in most people who have symptoms of reflux[21,22] and in those in whom reflux has been objectively determined using the standard acid reflux test.[21] Secondly, that the sphincter in people who have symptoms of reflux fails to respond to the challenge of an increase in intragastric pressure by an increase in sphincter pressure equal to or greater than the challenge.[6] If an antireflux repair is going to be effective in restoring cardioesophageal competence, it must at least improve both of these characteristic of an incompetent sphincter.

It is thought that by placing the lower esophagus into an intraabdominal position where it is in a positive pressure environment, a rise in sphincter pressure occurs. Indeed, this would seem to be the only mechanism by which the Hill repair raises the sphincter pressure. Our data oppose this concept since the Hill repair failed to statistically increase the amount of sphincter below the RIP, that is, amount of sphincter which is exposed to the positive pressure of the abdomen (Fig. 5). Anatomically, however, the Hill repair created an average of 3.1 cm of intra-abdominal esophagus (Table 1). To resolve this conflict it should be noted that preoperatively, in the presence of a hiatal hernia and therefore without an intra-abdominal segment of esophagus, an average of 2 cm out of a 4 cm sphincter was exposed to a positive environment (Fig. 5). This would indicate that the hernia sac allows transmission of positive abdominal pressure up to its insertion around the cardioesophageal junction. The question then arises: Is the transmitted positive pressure in the hernia sac equal to or less than the positive pressure in the abdomen? Moosa and associates[15] have shown that in monkeys who reflux the positive pressure exerted externally on the cardioesophageal junction is less than that exerted on the anterior gastric wall. In monkeys who did not reflux, the positive pressure exerted on the cardioesophageal junction was equal to or exceeded that applied on the anterior gastric wall. It is probable, therefore, that the reduction of the hernia and the creation of an intra-abdominal esophagus would place the distal esophageal sphincter in an environment of stronger positive pressure than when it was located in the hernia sac, and thus increase the resting sphincter pressure.

The sphincter pressure appears to be further increased if the intra-abdominal portion of the esophagus is buttressed by a gastric fundic wrap so that gastric pressure can be applied directly on the DES. This was shown by the higher sphincter pressure obtained with the Belsey and Nissen repairs over that of the Hill repair. The Nissen and Belsey repairs, according to this study, best accomplish the first principle of restoring cardioesophageal competency, that is, increasing the resting sphincter pressure.

The second principle of restoring cardioesophageal competence is constructing a sphincter which responds to the challenge of an increase in intragastric pressure by increasing its pressure to an amount which is equal to or greater than the gastric challenge. Alday and Goldsmith[1] have nicely shown that the transferring of acute increases in gastric pressure into the esophagus is diminished as one increases the degree of gastric fundic wrap around the distal esophagus. The greater the wrap, the greater the protection of transmitting an acute rise in gastric pressure into the distal esophagus. This work is supported by that of Butterfield[5] who performed a Nissen and Belsey repair on the esophagus and stomach removed from several cadavers. Once the repair was constructed, the stomach was filled with water and a pressure of 250 mm of mercury was applied to the stomach with the use of a sphygmomanometer cuff and the preparation was observed for evidence of leakage of water from the stomach into the esophagus. An evaluation of 10 Nissen and Belsey repairs so constructed showed a leak in three of the 10 Belsey repairs and no leak in the Nissen repairs. In two incidences the leak in the Belsey repairs was related to a posterior bulge of the esophagus in the area not supported by the gastric fundic wrap. It would appear on the basis of these observations and the improvement observed in the abdominal compression test (Fig. 6) that the Nissen repair best accomplishes the second principle of restoring cardioesophageal competence by having the ability to respond to a challenge of increase in intragastric pressure.

Conclusion

On the basis of this extensive study, it is concluded that the Nissen repair over against the Belsey Mark IV and Hill repairs best controls gastroesophageal reflux as measured objectively with the standard acid reflux test and 24-hour pH monitoring of the distal esophagus. The Nissen repair produces a competent cardioesophageal sphincter by increasing its resting pressure and improving its response to an increase in intragastric pressure. This is accomplished at the expense of temporary, mild, postoperative dysphagia and a 50% chance of being unable to vomit after the repair. It is recommended that the Nissen procedure become the procedure of choice for surgical therapy of gastroesophageal reflux.

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Discussion

Dr. Lucius Davis Hill (Seattle): I wish to compliment the authors on the utilization of objective measurements to assess our results for gastroesophageal reflux. Since we first reported the use of pH and pressure studies in 1961, we have been gratified that this technique has been employed across the country, and we would agree with the authors that it represents the most sensitive method of detecting reflux.

There are a couple of features that are of concern, however, in regard to the authors' depiction of the median arcuate repair. (Slide) It was disturbing that they achieved only a centimeter of esophagus below the diaphragm. We believe that the intra-abdominal esophagus is important in the prevention of reflux, and believe that dysphagia is related more to tightening of the gastroesophageal sphincter mechanism, or the esophageal introitus, rather than the length of esophagus below the diaphragm. If one visualizes the normal anatomy, the median arcuate ligament lies by direct measurement about 5 cm below the diaphragm. We generally end up with about 3 cm of esophagus below the diaphragm, and have not found that this creates dysphagia.

(Slide) We, too, are concerned about raising sphincter pressure intraoperatively three years following posterior gastropexy in of reflux is directly related to sphincter competence. In a small series of patients with stricture, the most severe complication of this disorder, we raised the sphincter pressure an average of 10 mm Hg. The authors demonstrated that they did not elevate the sphincter pressure with our procedure in three patients.

(Slide) To avoid leaving an inadequate sphincter, we started a year ago to measure the sphincter pressure intraoperatively. This, we think, is a real advance in surgery for hiatal hernia. The technique is simple and safe, and consists of placing a polyethylene tube attached to a nasogastric tube in the stomach. The polyethylene tube has a side opening 7 cm from the tip. During the operation the tube is passed through the sphincter before the repair to measure the prerepair sphincter pressure. Then the tube is passed again through the sphincter to measure the lower esophageal sphincter pressure (LESP) after the repair.

In 26 patients the mean preoperative LESP was 5.8 mm Hg. Following repair the intraoperative sphincter pressure was raised to a mean of 33 mm Hg. In all 26 patients reflux has been corrected, as evidenced by postoperative pH and pressure studies showing a mean postoperative sphincter pressure of 19.6 mm Hg and no reflux.

As far as we know, this is the first attempt to measure the sphincter pressure in the anesthetized human. We persist in calibrating and tightening the cardia at operation until we have a sphincter pressure that is in the proper range. We have tested ten normal patients with no known esophageal disease, and the pressure in the normal patient appears to be around 25 mm Hg intraoperatively.

We have had the opportunity to measure the sphincter pressure intraoperatively three years following posteriar gastropexy in a patient who returned for cholecystectomy. This patient had had a preoperative pressure of 5 mm Hg with gross reflux. The intraoperative sphincter pressure at the end of the three years is 24 mm Hg, and there is no reflux.

I think if the authors would admonish their chief surgical residents to adhere to these simple points of calibration of the cardia and obtaining adequate esophageal length, they would find that the median arcuate repair will correct reflux with a high degree of efficiency. I cannot resist saying that there is always a mystique about a foreign, imported product, such as the Belsey and Nissen procedures. But, I think if the authors would bear these simple techniques in mind the "home grown" median arcuate repair will look better than the foreign imports.

Dr. George V. Brindley, Jr. (Temple, Texas): This presentation provided a splendid evaluation of methods to correct esophageal reflux. I certainly agree that the abdominal Nissen fundoplication is an excellent procedure for correcting reflux.

I would like to add that there are some conditions in which the left transthoracic approach might be advantageous. I would prefer to use the left transthoracic approach if reflux esophagitis is persistent or recurrent; if the esophagus appears to be unusually short; or if other diseases of the esophagus (i.e., marked, diffuse spasm or epiphrenic diverticula associated with marked, diffuse spasm) should be corrected during the same operation. Although the Nissen method can be used above the diaphragm, it is technically more difficult than the left transthoracic approach, especially when transthoracic repair has already been attempted.

The Belsey Mark IV procedure is my preference for transthoracic herniorrhaphy. Cardiomyotomy may be added for the patient with marked, diffuse spasm or for one who has diffuse spasm associated with epiphrenic diverticula. The results have been good when the Belsey procedure has been adapted to each patient's individual needs. Recurrence of reflux esophagitis has been rare, and an effective lower esophageal sphincter has been restored.

DR. EDWARD ROY WOODWARD (Gainesville, Florida). Some four years ago we compared the old, traditional crural repair method with the Nissen fundoplication, and found, as one would expect, that the valvuloplastic method is considerably more effective in curing reflux esophagitis. We had a recurrence rate of 18% in 127 cases with crural repair, and 9% in 104 patients with the Nissen fundoplication.

The resting pressures in the lower esophageal sphincter closely parallel clinical success; namely, they about doubled in patients in whom the esophagitis was cured; and we found no difference between the two operations.

We have had difficulty quantitating motility tracings because of the variability in reading sphincter pressures in the same patient at the same time. This depends on the rotational axis of the pressure tip that's being used, and makes statistical comparison very difficult.

The Tuttle-Grossman method for the simultaneous measurement of pH and pressure is much too sensitive in terms of the pH profile, because a great many asymptomatic patients have demonstrable reflux. We feel the method used by the authors more closely parallels the *in vivo* situation.

I would raise a question as to the dependability of pressure profiles in measuring the relationship between the esophageal hiatus and the lower esophageal sphincter. The lower esophageal sphincter is not in a flat transverse plane in relationship to the body, and this makes, in the dog or in the monkey, as much as 1½ cm of difference in the relationship between these two structures.

In summary, we think the valvuloplastic principle is here to stay for the correction of gastroesophageal reflux. We have found the Nissen to be a very reliable method. However, the morbidity that we have observed with this procedure has been very real, although, in most patients, temporary; and in our hands we can achieve more satisfied patients with less morbidity using the method described by Dr. Hill.

DR. LLOYD M. NYHUS (Chicago): I rise for two reasons: First, to thank the authors for a very fine study; second, to voice our lack of understanding relative to the improvement in function in the distal esophageal sphincter following all three plasty procedures.

The valves created, particularly the Nissen and the Belsey, are mechanical in nature, and have no intrinsic physiological dynamic function. All three procedures effectively prevent reflux, the Nissen fundoplication being the most effective, as demonstrated again today.

The most attractive thesis for increase in function of the distal esophageal sphincter relates to the healing of the peptic esophagitis when reflux is stopped. Is reduction of the lower esophagus and stomach below the diaphragm important to this phenomenon? Dr. Bombeck and his colleagues have made observations which detract from these two attractive hypotheses.

(Slide) Here you see an animal experiment showing the normal positive pressure in the area of the sphincter, the rise in pH as the catheter is removed from the stomach up into the well protected esophagus.

(Slide) If you resect the distal esophageal sphincter in the dog, and then reanastomose, and then do these tests again, you have no pressure, and, of course, you have massive reflux. If, in this animal, you perform a Nissen fundoplication, (slide) you see, with the sphincter destroyed, that the Nissen is mechanical in nature and prevents reflux, and there is no dynamic action of this technique.

(Slide) In this patient, you see a number of normal controls of the distal esophageal sphincter pressure, running about 18 to 20. In a group of patients who were treated medically, pretreatment their sphincter pressures were down somewhat—maybe not statistically significant—but after cure of their esophagitis by medical treatment, there certainly was no increase in the sphincter pressure in this group of patients.

Finally, here we see our own group of patients, pre- and post-Nissen, showing the classic depression of the distal esophageal sphincter pressure preoperatively, and the rather nice pressure change toward positive postoperatively.

May I remind you that we do not usually repair the crus, and that one-half of the patients in the postoperative period had their esophagastric junction above the diaphragm.

Thus we have seen a failure to improve distal esophageal sphincter function following healing of esophagitis by medical treatment. We have seen improvement in distal esophageal sphincter function when the esophagogastric junction has rested above the diaphragm, following the Nissen fundoplication. We remain perplexed. Can the authors shed more light on this vexing problem?

DR. T. R. DEMEESTER (closing discussion): In reference to Dr. Hill's comments concerning the fact that insufficient esophagus was brought down into the abdomen, we would agree that this is true when measurements are based on manometric studies, but anatomically based on the postoperative upper GI radiographic study done on these patients, an average of 3.1 cm of distal esophagus was placed within the abdomen. So, there *is* a difference between anatomic intraabdominal esophagus and functional intraabdominal esophagus, that is, the amount of distal esophagus exposed to the positive pressure environment of the abdomen.

Dr. Hill also mentioned that the elevation of the DES pressure did not occur in two of our patients who received a Hill repair, and that if we would concentrate on improving the DES pressure, the results of the Hill procedure would improve. It has been our experience that the DES pressure does not always relate to competence of the sphincter. Some people can have low pressures and have a very competent sphincter, and the reverse can be true. We do agree, however, that a good sphincter is an important aspect in preventing reflux, but there is not a one-to-one correlation between sphincter pressure and the presence of reflux, as objectively measured. Indeed, there was no correlation between the pre- and postoperative change in sphincter pressure seen in these patients and how they did on the pH study. The two patients referred to by Dr. Hill, who had a drop in DES pressure postoperatively, had competent sphincter on 24-hour pH monitoring.

I believe that when we plan an operative procedure directed toward the goal of restoring cardioesophageal competence, the end point should be to restore competence, not necessarily an elevated sphincter pressure. The restoring of competence can be best measured by pH studies.

In regard to Dr. Brindley's comments, I would agree with him about the choice of the thoracic approach in those conditions where it is indicated. Of interest is that we have used the thoracic approach for a Nissen repair in situations that he has indicated and were surprised to find that these patients have very little dysphagia postoperatively and their esophageal length did not increase, as is seen after the abdominal approach. This would suggest that the mobilization of the distal esophagus, done during the thoracic approach, prevents the necessity of stretching the esophagus in order to place the repair within the abdomen and, therefore, limits the amount of postoperative dysphagia.

In regard to Dr. Woodward's comments, I agree with him about the technique of measuring pressures, and I might state that these pressures were measured using a perfused catheter consisting of three lumens, with lateral holes placed 5 cm apart at the distal end. DES pressure was measured as the pressure difference between the end expiratory gastric pressure and the pressure in the sphincter at the point of respiratory reversal. There were three measurements for each patient, and the average of the three was the value reported.

Dr. Woodward also commented regarding the questionable reliability of manometry measurement as an indication that more of the sphincter is in the positive pressure of the abdomen after surgical repair. We feel that this measurement is reliable and important. Drs. Nagler and Spiro have shown that in pregnant females the portion of the sphincter which is in the abdomen is lost, and this occurs at the time the patient has symptoms of reflux. He stresses the fact of having 1–2 cm of the 4-cm sphincter in the positive pressure environment, allowing this portion of the sphincter to respond to increases in intraabdominal pressures, as an important aspect of the competent sphincter.

Dr. Woodward also commented on the morbidity of the Nissen procedure. We have not seen the degree of morbidity he has reported. Perhaps, the difference lies in how the Nissen repair is done. We do not extend the wrap more than 3–4 cm over the distal esophagus, using only four sutures, and do the wrap over a 30 French gastric tube. We feel that a longer or tighter wrap results in a supercompetent sphincter and the morbidity he mentioned.

Dr. Nyhus commented nicely on all the problems in trying to interpret how the changes in manometric studies are responsible for producing a competent sphincter. How does this sphincter work? It is our feeling that there are two factors of importance in producing a competent sphincter. One is that you must increase the sphincter pressure, although it is not a one-to-one relationship, and we have seen using our pH studies that if the sphincter pressure is over 20, there is little chance for reflux to occur. The second factor that seems to be important in producing a competent sphincter was pointed out by Drs. Cohen and Harris. They have shown that a competent sphincter must have the ability to respond to an increase in intragastric pressure to an amount that is equal to or greater than the gastric challenge. Otherwise, the pressure resistance of the sphincter is exceeded and reflux occurs. The Nissen procedure does increase the sphincter pressure, and studies reported in the manuscript show it also improves the ability of the sphincter to respond to increased intragastric pressure. Perhaps, both of these changes come about by its ability to significantly increase the amount of DES exposed to the positive pressure environment of the abdomen.

Surgical Management of Reflux Gastritis

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Reflux gastritis is now recognized with increasing frequency as a complication following operations on the stomach which either remove, alter, or bypass the pyloric phincter mechanism. The entity may occasionally occur as a result of sphincter dysfunction in the patient who has not undergone prior gastric surgery. The diagnosis is made on the basis of symptoms (postprandial pain, bilious vomiting and weight loss), gastroscopic examination with biopsy and persistent hypochlorhydria. Remedial operation for correction of reflux is indicated in the presence of persistent symptoms when conservative measures fail. Only operative procedures which divert duodenal contents from the stomach or gastric remnant are effective. Both the isoperistaltic jejunal segment (Henley loop) and the Roux-en-Y diversion have been effective as remedial operations for reflux gastritis and merit greater awareness by gastroenterologists and surgeons. Our choice is the Roux-en-Y because of its technical simplicity and lower morbidity rate.

BILIOUS VOMITING was recognized as a complication of gastric surgery shortly after Anton Wolfler[61] performed the first gastroenterostomy in 1881. The complication was likewise appreciated following the introduction of the Billroth II method of gastric resection in 1885.[8] As a result, surgeons during the next several decades devised various types of gastroenteric anastomoses in hopes of obviating this distressing complication.[25] With the advent of gastroscopy, Hurst[32] and Schindler[52–54] were among the first to comment upon the relationship between gastroenteric stomas and gastric mucosal atrophy. Palmer,[45,46] studying by gastroscopy the effects of gastric operations on the gastric mucosa, described gastritis as a frequent complication, but felt the inflammatory changes were in part a natural progression of the pre-existing state. Other observers,[6,40] utilizing gastric biopsy, reported high instances of gastritis following gastric resection.

During the past two decades an increasing number of investigators and clinical surgeons[3,5,11,13,16,19,21,30,35,37,41,58,62] have recognized a symptom complex which has been termed alkaline reflux gastritis. This complication occurs in varying degree in 5–35% of patients who have undergone gastric surgery in which the pyloric sphincter mechanism was either removed, bypassed, or rendered incompetent. The symptoms are separate and distinct from the vasomotor and gastrointestinal disturbances of dumping and other postgastrectomy syndromes, and consist of diffuse upper abdominal pain, nausea and vomiting of bile stained material, weight loss, and gastrointestinal bleeding in some instances. The patients are usually achlorhydric by standard gastric analysis.

Within the past decade the widespread use of the fiberoptic gastroscopy, gastric biopsy, and electron microscopic study of gastric mucosa has increased our understanding of the pathophysiology of this condition. It has now been documented by pyloric pressure measurements and gastroscopic studies that some patients with intact stomachs may experience symptomatic reflux gastritis. It is further appreciated that bile and duodenal contents may be present in both the intact and postoperative stomach without producing deleterious effects. Likewise, documented gastritis may exist in the absence of clinical symptoms[23,24,27,31,33] as only a few patients demonstrate this hypersensitivity to bile reflux.

Mild symptoms of reflux gastris can be managed effectively by conservative measures consisting of diet, antispasmodics, and cholestyramine which has proven effective in some instances.[2,56] However, if appreciable

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symptoms exist, conservatism is fraught with failure and remedial operation is indicated. Experience has shown that only procedures which divert bile completely from the stomach are effective in alleviating both symptomatology and gastric mucosal changes.

The purpose of this communication is to relate a nine-year experience with 48 patients who underwent either a Roux-en-Y diversion or a Henley loop operation for severe symptoms of reflux gastritis which were not controlled by the usual nonoperative treatment. The operative management of this group of patients will be discussed along with followup results. A clinical appraisal of the two remedial procedures will be made.

Clinical Study

Of the 48 patients who underwent remedial operation for correction of reflux gastritis, 31 were men and 17 were women. The ages ranged from 10 to 81 years with most of the patients between 30 and 59 years of age. The original operation was performed for duodenal ulcer in 44 patients, stress ulceration in one patient, and a high lying gastric ulcer in one patient. Ten of the 48 patients had originally been subjected to bilateral truncal vagotomy-antrectomy and gastroduodenostomy (Billroth I). Seventeen patients had previously undergone truncal vagotomy-gastric resection and a Billroth II type reconstruction. Eleven patients had as the original operation a gastric resection of the Billroth II type without vagotomy. Seven patients had undergone a vagotomy and drainage procedure of which five were pyloroplasties and two were gastroenterostomies. One patient had been subjected to gastroenterostomy alone, and two patients had not had previous gastric surgery (Fig. 1).

The time interval between the original operation for ulcer and the onset of symptoms of reflux gastritis varied from a few weeks up to 20 years. Eighteen patients noted symptoms of reflux within 6 months, 13 patients experienced symptoms within 2 years, and 17 patients experienced a symptom-free interval ranging from 7 to 20 years.

Epigastric pain, unrelieved by antacids, was a presenting symptom in all patients. The pain was usually made worse by food, thus restricting the oral intake with resultant weight loss. Nausea and vomiting were also experienced by each patient. The emesis was bile stained in most instances and was particularly annoying in the recumbent position and frequently interfered with sleep. Weight loss developed in 31 patients and ranged from 10 to 50 pounds, with an average weight loss of 23 pounds. Anemia of a microcytic hypochromic type was present in 19 patients. Six patients presented with gastrointestinal bleeding, and each required several transfusions while undergoing preparation for remedial surgery (Fig. 2). Gastric secretory studies, when done, revealed achlorhydria during fasting and following histalog stimulation in each patient who had undergone prior gastric surgery. The two patients who had not undergone previous gastric surgery demonstrated achlorhydria during fasting but showed a low acid response to histalog. Gastrointestinal barium studies failed to demonstrate a recurrent ulcer, stomal dysfunction, or other abnormalities among the entire group.

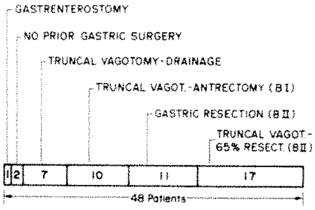

FIG. 1. Original operative procedures in the 46 patients who subsequently developed reflux gastritis. Two patients had not undergone prior gastric surgery.

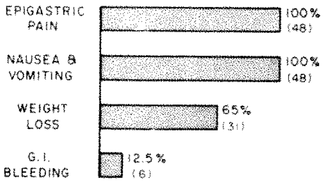

FIG. 2. Symptoms experienced by the 48 patients.

On gastroscopic examination duodenal content containing bile could be seen regurgitating into the gastric remnant and numerous bile lakes were scattered over the mucosa, which was usually granular, friable, and atrophic in appearance. The presence of multiple small superficial ulcerations was a frequent finding. Gastric mucosal biopsies demonstrated variations in the severity of the inflammatory process among the patients. No corrulation, however, could be made comparing patient symptomatology with the extent of the gastric mucosal changes. Biopsy studies among the patients varied from a picture of acute focal mucosal hemorrhage with an inflammatory infiltrate in the lamina muscularis mucosa to superficial mucosal ulceration (Fig. 3). Reduction in mucosal thickness was noted along with chronic inflammatory infiltrates. Parietal and chief cell dimunution was also apparent along with an increase in mucous secreting cells.

Cholestyramine was used in 10 patients in an attempt to remove the bile reflux but without significant benefit. The drug is given in granular form, is expensive, and is poorly tolerated. No patient had received ulcerogenic medications and alcohol was not a problem among the group.

Remedial Procedures

Two different remedial operations, each directed toward preventing bile and duodenal contents from entering the gastric remnant or stomach were utilized in the 48 patients. A Roux-en-Y diversionary operation,

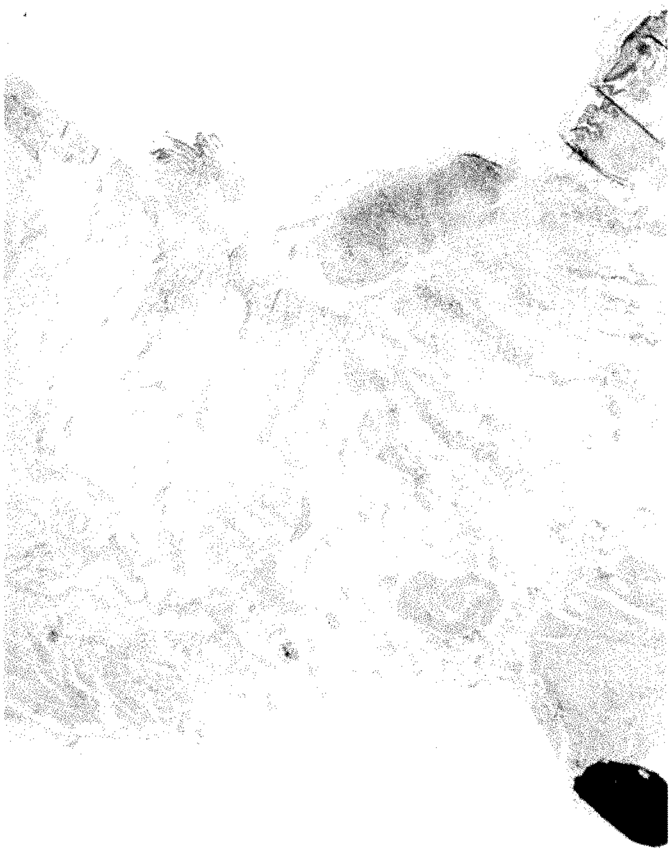

Fig. 3. Gastric mucosal biopsy showing an area of superficial mucosal ulceration and a chronic inflammatory infiltrate in the lamina muscularis mucosa.

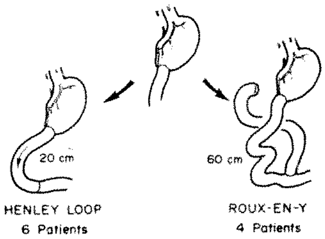

Fig. 5. Type of remedial operation carried out in 10 patients who originally underwent vagotomy-antrectomy-Billroth I.

or a modification thereof, was carried out in 27 patients and an interposed isoperistaltic jejunal segment between the gastric pouch and duodenum (Henley loop), was used in 20 patients. One patient who had undergone a simple gastroenterostomy for an alleged duodenal ulcer 20 years prior had the gastroenterostomy dismantled and no other gastric surgery performed as the duodenum was normal (Fig. 4).

Of 10 patients who originally underwent truncal vagotomy-antrectomy and a Billroth I reconstruction for ulcer disease, six were subjected to the remedial operation consisting of a Henley loop (utilizing an interposed jejunal segment, 20 cm. in length) and four underwent a Roux-en-Y diversion (Fig. 5).

Of 17 patients who initially underwent truncal vagotomy-gastric resection and a Billroth II reconstruction, five were converted to a Henley loop interposition, seven had a Roux-en-Y diversion, a Hunt-Lawrence pouch with a Roux-en-Y diversion was used in four, and a Valdoni circular loop was constructed and connected to the duodenal outflow tract in one patient. In this group the gastroenteric stoma was left intact in construction of the Henley loop operation and the Soupault-Bucaille maneuver was employed (Fig. 6).

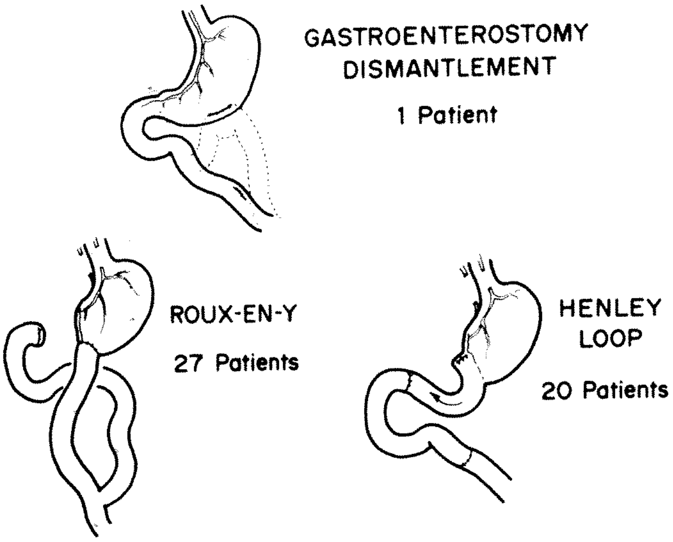

Fig. 4. Remedial operations done in the group of 48 patients.

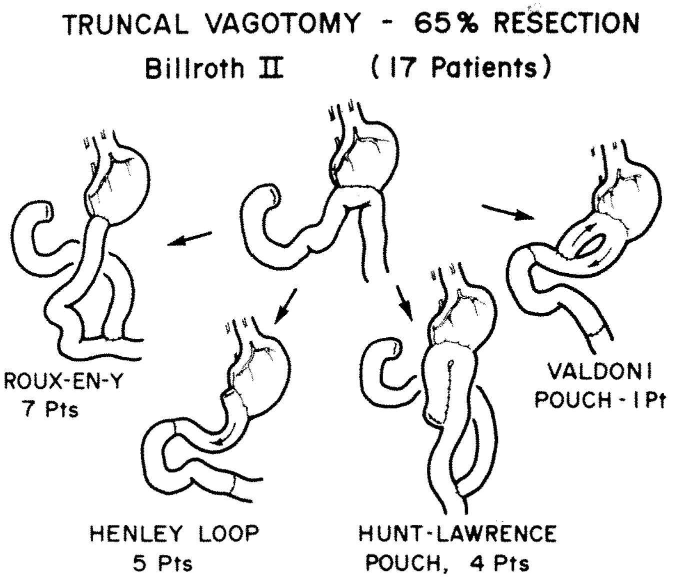

Fig. 6. Remedial procedures performed in 17 patients who originally had vagotomy-resection-Billroth II.

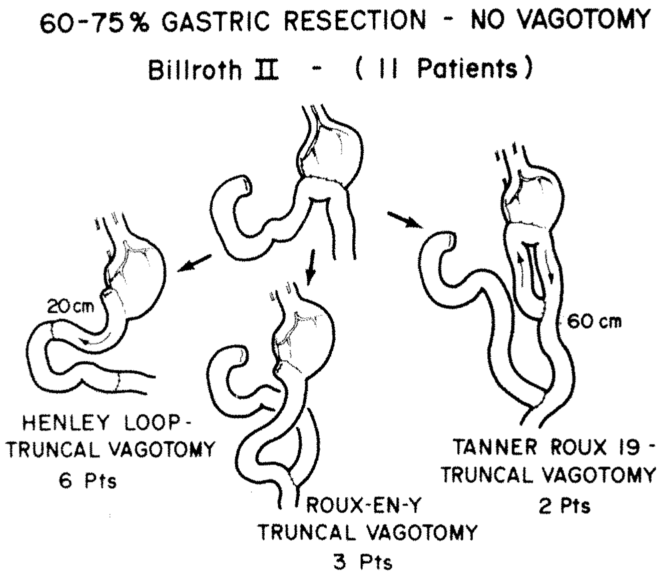
60-75% GASTRIC RESECTION - NO VAGOTOMY
Billroth II - (11 Patients)
20 cm
HENLEY LOOP - TRUNCAL VAGOTOMY 6 Pts
ROUX-EN-Y TRUNCAL VAGOTOMY 3 Pts
60 cm
TANNER ROUX 19 - TRUNCAL VAGOTOMY 2 Pts

FIG. 7. Remedial operations in 11 patients who originally underwent gastric resection without vagotomy.

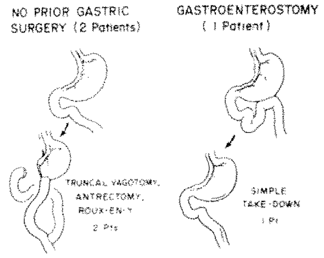
NO PRIOR GASTRIC SURGERY (2 Patients)
GASTROENTEROSTOMY (1 Patient)
TRUNCAL VAGOTOMY, ANTRECTOMY, ROUX-EN-Y 2 Pts
SIMPLE TAKE-DOWN 1 Pt

FIG. 9. Two patients having had no prior gastric surgery treated by vagotomy-antrectomy and Roux-en-Y. One patient had simple gastroenterostomy dismantlement.

Eleven patients had originally undergone an estimated 60–70% Billroth II gastrectomy without vagotomy. Among six of this group the remedial operation consisted of a Henley loop procedure with addition of truncal vagotomy. Three patients were converted to a Roux-en-Y diversion and two patients underwent a circular loop pouch construction with a Roux-en-Y diversion (Tanner 19). Each of the five patients also had bilateral truncal vagotomy performed (Fig. 7).

Of seven patients who had undergone vagotomy with drainage as the initial operation, five were subjected to antrectomy and Roux-en-Y reconstruction. Two patients underwent antral resection and insertion of a 20 cm Henley loop (Fig. 8).

Two patients who had not had previous gastric surgery were treated by truncal vagotomy-antrectomy and Roux-en-Y reconstruction. The one patient with a simple gastroenterostomy underwent dismantling of the gastroenterostomy with reconstruction of the intact stomach (Fig. 9).

Hospital Course

A total of 16 patients who originally underwent a Billroth II type resection with or without vagotomy were subjected to Roux-en-Y diversion. There was no significant complication in this group and the postoperative hospital stay averaged 8 days. Of the 12 patients with a Billroth II reconstruction with or without vagotomy subjected to a Henley loop procedure using the Soupault maneuver, nine experienced an uneventful recovery, but three patients developed transient fullness, stasis, and delayed gastric emptying which was alleviated with nasogastric decompression. The postoperative hospitalization averaged 11 days (Figs. 10–12).

Of four patients who underwent Roux-en-Y diversion following truncal vagotomy-antrectomy and Billroth I reconstruction, one developed prolonged gastric emptying which responded to additional nasogastric suction. The hospital stay among this group averaged 11 days. On the other hand, of six patients subjected to a Henley loop procedure following vagotomy-antrectomy and a Billroth I reconstruction, five experienced fullness following removal of the nasogastric tube, and normal emptying did not take place for at least two weeks (Figs. 13–16).

Of the seven patients who originally underwent vagotomy with drainage, five who subsequently had Roux-en-Y diversion with antrectomy experienced less postoperative morbidity than the two patients subjected to antrectomy with Henley loops (Fig. 17).

The two patients without a prior gastric operation treated by vagotomy-antrectomy with a Roux-en-Y diversion had uneventful postoperative courses. The one patient with the gastroenterostomy dismantlement experienced no complications.

Results

The followup after remedial operation among the 48 patients ranges from 6 months to 9 years. There was no

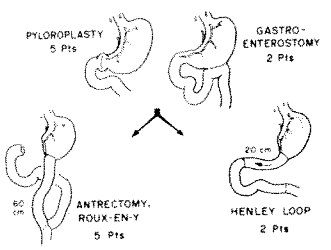

FIG. 8. Remedial operations in seven patients following the original procedure of vagotomy with drainage.

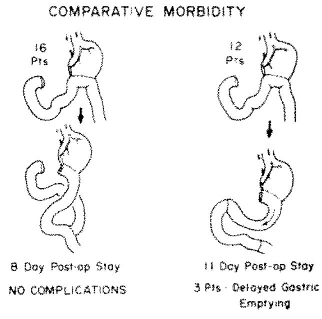

FIG. 10. Conversion from a Billroth II type anastomosis to Roux-en-Y was associated with less morbidity than conversion from a Billroth II to a Henley loop.

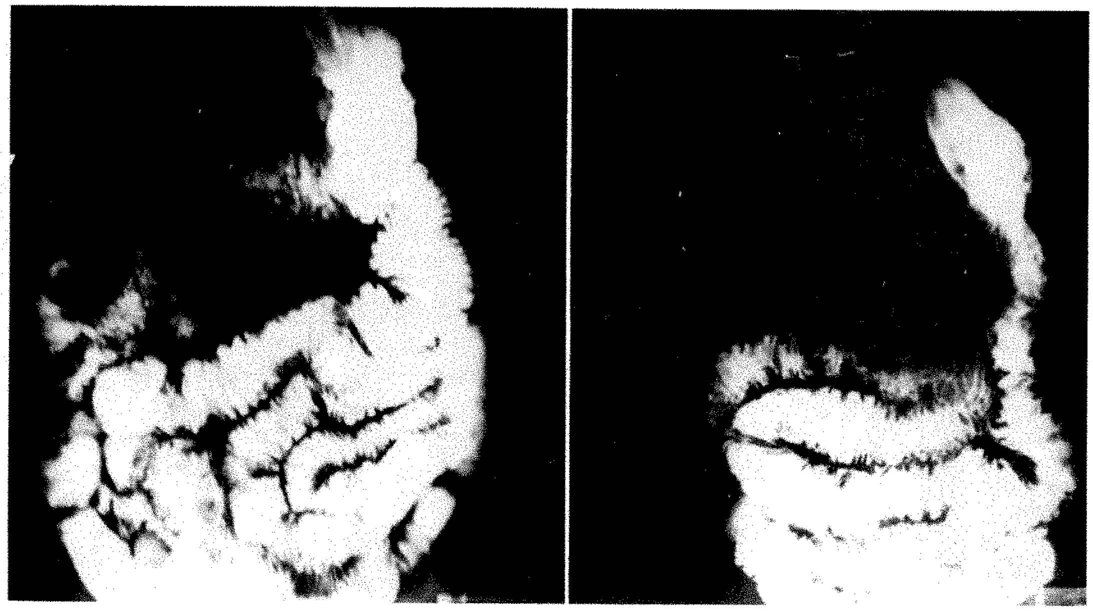

FIG. 11. (Left) Barium study following Billroth II reconstruction. (Right) Conversion to Roux-en-Y showing normal emptying with no dilatation of the gastric pouch. No emptying problems occurred in 16 patients.

operative mortality but one late death occurred from myocardial infarction. Of the 27 patients comprising the Roux-en-Y group 17 have obtained an excellent clinical result, and a good result has occurred in 10. The patients comprising the latter group note occasional fullness and mild discomfort but epigastric pain and nausea and vomiting have been completely relieved. There was essentially no difference in the results between men and women patients. Among the 20 patients in the Henley loop group, 14 have obtained an excellent result and four are graded a good result. One patient continues to note epigastric discomfort and vomits occasionally. He has been graded a fair result. One patient has been termed a poor result as he continues to experience nausea and vomiting at times which could be related to the dumping syndrome. He still shows a 25 pound weight loss which occurred following the original vagotomy and antrectomy and Billroth II reconstruction. He is also anemic but repeat gastroscopic studies demonstrate improvement in the degree and extent of gastritis (Fig. 18). Conversion from a Henley loop to a Roux-en-Y as reported by Woodward has not been necessary.[63]

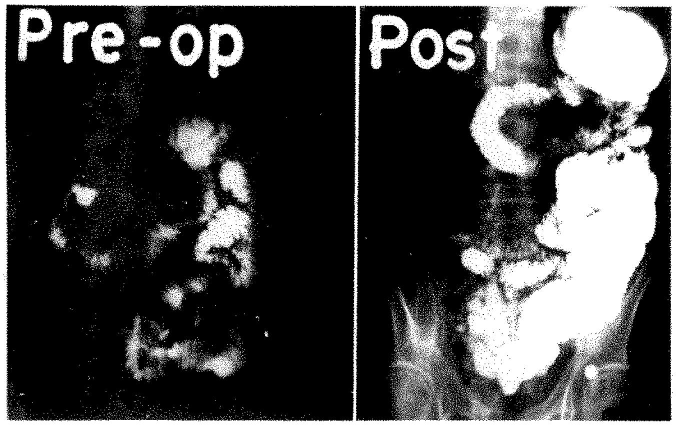

FIG. 12. (Left) Original Billroth II reconstruction with a small gastric pouch. (Right) Barium study in the early postoperative period after conversion to a Henley loop shows some gastric pouch dilatation and stasis.

Of the 31 patients among the 48 who lost weight after the onset of symptoms of reflux gastritis, weight gain has occurred in 17, with one patient showing a weight gain of 50 pounds. Weight gain has taken place in 11 patients who underwent a Roux-en-Y diversion and in six patients with Henley loops. The four patients with a Hunt-Lawrence pouch and Roux-en-Y diversion had each lost considerable weight prior to the remedial procedure and a weight gain of 10–40 pounds has taken place among the four patients. The single patient with the gastroenterostomy dismantlement has gained 20 pounds and is free of symptoms. The one patient in the group alluded to who underwent a Henley loop procedure and died of unrelated causes 8 months later, obtained a good result.

The relief of abdominal pain and bile stained vomiting

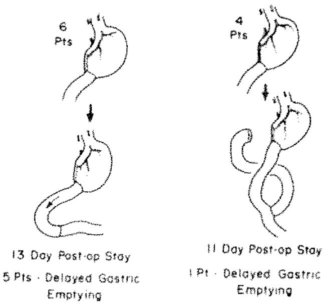

FIG. 13. Conversion from a Billroth I anastomosis to Roux-en-Y was also associated with less morbidity than conversion from a Billroth I to a Henley loop.

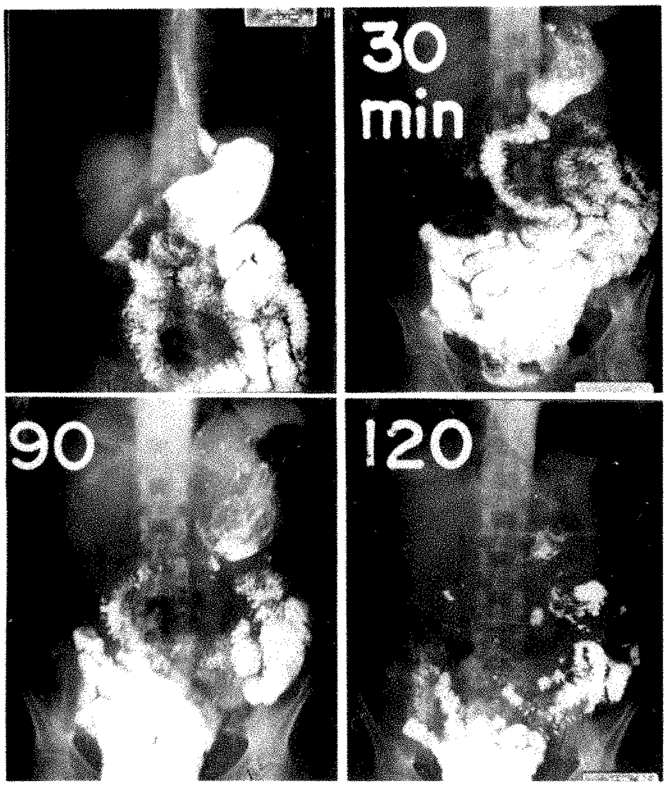

FIG. 14. Roux-en-Y remedial procedure following an original vagotomy-antrectomy-Billroth I. Barium study shows no evidence of gastric pouch stasis.

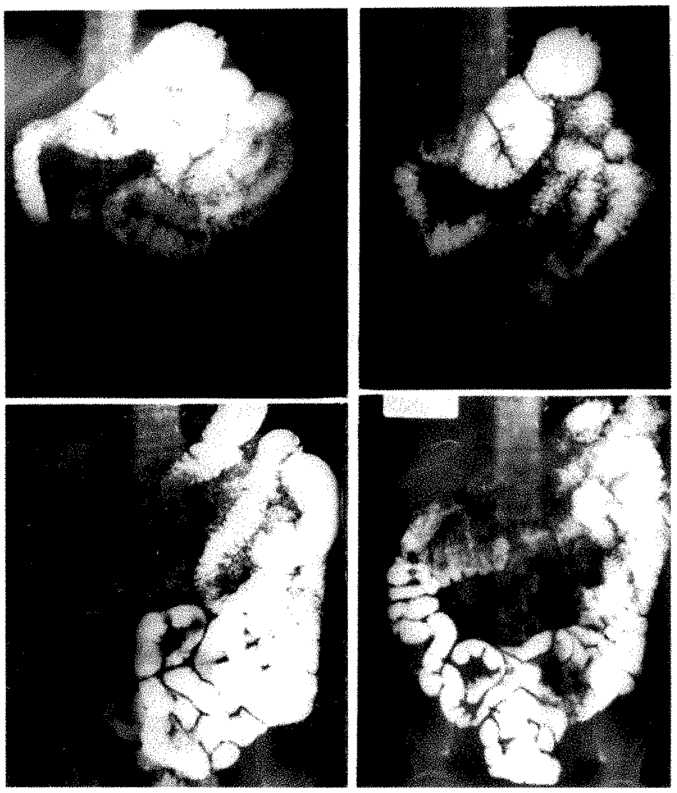

FIG. 16. Barium study *several weeks* postoperatively showing no evidence of stasis in the gastric pouch or isoperistaltic jejunal segment (Henley loop).

has been dramatic in the group and is readily apparent during the early postoperative period. The symptomatic improvement is also associated with marked improvement in the endoscopic appearance of the gastric mucosa.

Discussion

It has been recognized for many years that varying degrees of gastritis occur after both simple gastroenterostomy and a Billroth II gastric resection. With increasing use of the Billroth I method and also pyloroplasty in the past two decades, it has become apparent that gastritis may likewise follow these procedures. Prior

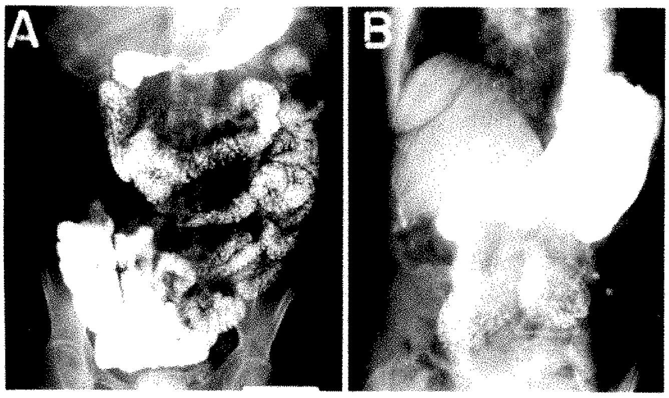

FIG. 15. (A) Barium study showing Billroth I reconstruction with antrectomy. (B) Conversion to Henley loop interposition procedure in the early postoperative period demonstrating marked dilatation and stasis in the gastric pouch. Clinical symptoms of stasis were present.

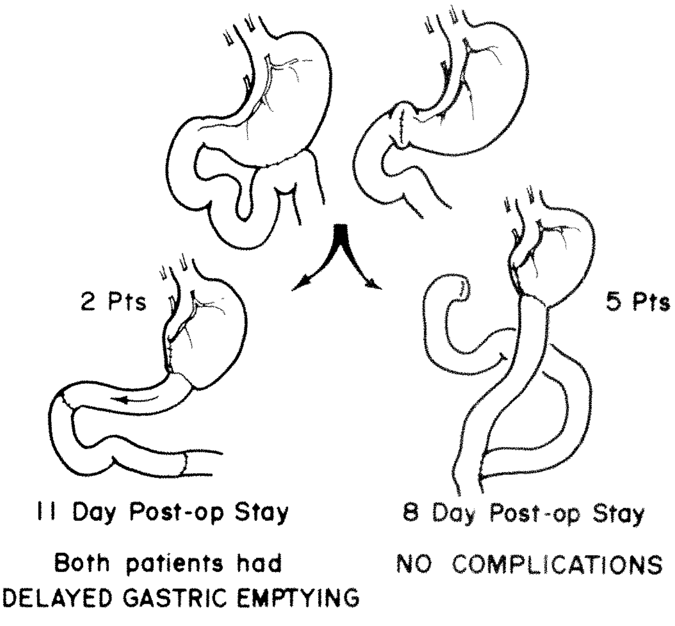

FIG. 17. With vagotomy and drainage, patients converted to Roux-en-Y experienced less morbidity than patients with Henley loops.

	EXCELLENT	GOOD	FAIR	POOR
ROUX-EN-Y (27 Pts)	17	10	0	0
HENLEY LOOP (20 Pts)	14	4*	1	1
GASTROENTEROSTOMY DISMANTLEMENT (1 Pt)	1	0	0	0

*1 death 8 months post-op of unrelated causes.

FIG. 18. Results with the two remedial operations for treatment of reflux gastritis.

to 20 years ago both the clinical significance and the pathophysiology of reflux gastritis were pooly understood. Mimpress and Birt,[43] and Roux *et al.*[51] theorized that bile emesis represented either stomal, afferent, or efferent loop obstruction. Indeed, some patients were even labeled as suffering from psychoneurosis.

During the past two decades several British and South African investigators[15,22,39,58,60] have documented the fact that in susceptible persons emesis of duodenal contents may result from accumulation of bile and pancreatic secretions in the postoperative stomach in the absence of obstructive phenomena. Lawson[37] was among the first to demonstrate experimentally both inflammatory and proliferative changes in the canine gastric mucosa following various gastric procedures designed to allow duodenal secretions, bile, and pancreatic juice to come into contact with the gastric mucosa. Gastric mucosal changes were most prominent with a combination of bile and pancreatic juice, less striking with bile alone and even less pronounced with pancreatic juice. Lawson[38] further showed that diversion of the total duodenal content into the stomach produced an extensive degree of gastritis, greater than that observed after gastroenterostomy or pyloroplasty. In operations where the pyloric antrum was removed, reflux gastritis extended far into the gastric remnant, but in gastric procedures which preserved the antrum, the gastritis was less extensive.

Lawson[36] in classical experiments demonstrated that atrophic gastritis with disappearance of parietal and chief cells occurred in the fundic mucosa following both a Billroth I and Billroth II resection. Despite excision of the alkaline antral area, a new alkaline zone developed in the gastric pouch. Capper,[11] aside from studying the histology of the gastric mucosa in the postresection state, estimated the altered pH of the mucosa and, due to replacement by mucous secreting cells, found the residual gastric mucosa highly alkaline. In patients with a Roux-en-Y reconstruction, however, he observed that the gastric mucosa remained acid secretory in type down to the gastrojejunal anastomosis.

DuPlessis[20,22] was one of the first investigators to study the effects of duodenal reflux in patients with atrophic gastritis and gastric ulcer. He found the concentration of bile acid conjugates in fasting aspirates of patients with gastric ulcer to be normally high. Black[9] noted that fasting and postprandial bile acid concentrations were higher in patients with atrophic gastritis and gastric ulcer than in normal individuals. Rhodes,[48] employing radioactive-tagged bile salts and measuring the concentration of radioactive bile salts in the postprandial gastric aspirate, found that in patients with gastric ulcer, duodenal regurgitation was greater than in normal controls. Cheng, Delaney and Ritchie[14] conducted experiments in which tubes of gastric wall with intact vasculature were fashioned from the greater curve of the dog's stomach and interposed at various sites in the gastrointestinal tract and biopsied at intervals. Exposure of the gastric wall to jejunal contents led to rapid and profound mucosal inflammatory changes with loss of both parietal and chief cells. Exposure of the wall to ileal content produced a similar effect. On the other hand, exposure of the gastric wall to pancreatic juice resulted in morphological changes but they were milder and slow to develop. These authors also demonstrated a marked loss of both parietal and chief cell mass after Billroth II type resection along with an increase in mucous secreting structures. These changes were not apparent in Billroth I cases up to one year.[18,49,50]

Menguy and Max[42] anastomosed the gastric antrum to the gallbladder in 14 animals and subsequently demonstrated severe inflammatory and proliferative changes in the antral mucosa. Beyers and Jordan,[7] however, were unsuccessful in their attempts to show that bile *alone* produced gastritis. Davenport,[17] using irrigations of bile and bile salts, demonstrated disruption of the gastric mucosal barrier with back diffusion of hydrogen ions and subsequent release of pepsin into the gastric lumen with resultant gastritis. Skillman[57] has described disruption of the gastric mucosal barrier in shock subjects, and Hamza[26] feels that bile salts contribute to the formation of gastritis and ulceration in experimental shock. Many observers currently feel that in addition to alterations in the protective qualities of gastric mucous produced by alkaline reflux, acid must be present in the stomach or gastric remnant for gastritis and ulceration to occur.

The exact biological and biochemical mechanisms whereby duodenal contents produce diffuse and/or atrophic gastritis with resultant ulceration have not been accurately defined. Apparently, however, the presence of both bile acid conjugates and pancreatic juice are necessary to produce significant changes. Recently both Bedi[4] and Nahrwold[44] have demonstrated that both bile and bile salts in low concentrations result in antral gastrin release. Thus, gastrin may perhaps be an additional contributing factor in producing gastritis and ulceration. Others think that gastrin may have a trophic effect on the gastric mucosa and exert a protective action by "tightening the mucosal barrier."[63]

More recently Fisher[24] has studied alterations in pyloric sphincter pressures in patients with increased duodeno-gastric reflux, gastritis, and ulceration. Upon stimulation such patients showed no change in sphincter response to either endogenous intraduodenal stimuli or exogenous administration of secretin or cholecystokinin. This was in sharp contrast to normal subjects. Capper[12] has likewise described a test to detect pyloric regurgitation.

Lately it has been suggested by Anderson[1] that parenteral hyperalimentation be used as a diagnostic test to further document reflux gastritis as being responsible for patient symptomatology. Total parenteral hyperalimentation results in a marked decrease in both biliary and pancreatic flow, and the authors postulated that in the presence of diminished flow both symptomatic and histologic improvement should take place. Their results showed that following institution of therapy, symptoms improved, reflux reduced, and parietal cell mass increased in two of three patients. The test was felt to be useful in evaluating surgical candidates and as supplementary preoperative support for patients who were malnourished.

Only operative procedures designed to divert duodenal and proximal jejunal contents from the stomach or gastric remnant have proven satisfactory in correcting symptoms of gastric reflux. Roux-en-Y diversion with or without a complimentary pouch reservoir or a Henley loop procedure appear to be effective. In our series of 48 patients the long-term results with the two procedures were comparable. From a survey of the literature many surgeons[3,10,15,16,19,34,39,47,55,59,60] currently prefer a Roux-en-Y diversion with a defunctionized jejunal limb 45–60 cm long.[55] With increasing interest and appreciation that reflux gastritis may be a distressing complication of definitive operation for ulcer, DuPlessis[22] has proposed for consideration the use of a Roux-en-Y limb as the method of reconstruction in primary operations for gastric ulcer. Both Henley[29] and Hedenstedt[28] have used a Henley loop in combination with vagotomy and partial gastrectomy as a primary operation for both gastric and duodenal ulcer.

The advantage of the Roux-en-Y technique is its technical simplicity, particularly if the original gastric procedure was a Billroth II type resection. The simple maneuver of shifting the afferent jejunal limb to the efferent limb, leaving the gastrojejunostomy undisturbed, has been associated with very little postoperative morbidity in most reported studies.

Patients undergoing a Roux-en-Y diversion following an original Billroth I reconstruction have experienced increased postoperative morbidity when compared to those patients undergoing Roux-en-Y diversion following an original Billroth II type resection. Take-down of the original gastroduodenostomy in the Billroth I procedure and conversion to end-to-end gastrojejunostomy resulted in delayed gastric emptying in one of four patients in our study. Conversion of a Billroth II type resection to a Henley loop procedure, although leaving the gastroenterostomy intact, still possesses the disadvantages of dissecting out and reopening the duodenal stump and the construction of two anastomoses. The morbidity in this group was greater when compared to patients undergoing a Roux-en-Y diversion after a Billroth II type resection.

Construction of a Henley loop after an original Billroth I reconstruction poses a more complicated problem and increased morbidity occurred with this group. The remedial procedure, of course, entails take-down of the gastroduodenostomy and the construction of three separate anastomoses. The interposed jejunal segment placed in its new domain may also require several days to several weeks for physiological adjustments to take place, and early emptying problems are frequent. Nasogastric suction was maintained in our group of six such patients for four to five days, and it was not unusual for such patients to experience abdominal fullness and early satiety for several weeks postoperatively.

Patients who originally underwent vagotomy with drainage and later Roux-en-Y diversion with antrectomy experienced less postoperative morbidity than such patients subjected to antrectomy with Henley loops. After a few weeks, however, in the vast majority of instances, with either remedial procedure epigastric fullness subsides and the patients are able to eat a normal meal. Radiographic studies show a return of the gastric remnant to normal. In performing either remedial operation we prefer to remove the gastric antrum because each procedure is ulcerogenic. Complete gastric vagotomy is obligatory.

It is our current feeling that the clinical entity of reflux gastritis is being diagnosed with increasing frequency. However, extreme caution should be exercised in not ascribing the symptoms of other postgastrectomy or postpyloroplasty sequelae to reflux gastritis. Likewise, the mere documentation of duodenogastric reflux, the presence of bile in the stomach, or reflux gastritis of mild degree with minimal symptomatology does not constitute an indication for remedial surgery. However, we share the feeling of other observers that in carefully selected patients with characteristic and sustained symptomatology documented by gastroscopy, biopsy, and persistent hypochlorhydria, that remedial operation is indicated. In our 48 patients the postoperative clinical results have been gratifying.

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Discussion

Dr. Carl P. Schlicke (Spokane): One's first reaction on hearing this paper is to wonder how anyone could accumulate 48 patients who required surgical intervention for the relief of alkaline gastritis. However, those who had the privilege of hearing Dr. Herrington's presentation before the Western Surgical Association in 1972, in which he reported a 25-year experience with vagotomy and antrectomy performed on 3584 patients, realize what an extraordinarily large experience with gastric surgery he and his colleagues have enjoyed.

Secondly, in spite of the number of investigators who in the past 20 years have called attention to reflux gastritis as a cause of postoperative distress, it is surprising how seldom the condition is recognized. In the first edition of the "gastric gospel" by Harkins and Nyhus, which appeared in 1962, the subject receives only cursory mention, and no allusion to it appears in any of the Yearbooks of Surgery since that time.

The bilious vomiting and nocturnal regurgitation so characteristic of reflux gastritis may erroneously be attributed to operative production of an incompetent cardioesophageal mechanism, whereas the true fault lies in the disruption of the pylorus. Attempts to restore the physiologic status of the structures in the vicinity of the esophageal hiatus, obviously, are of no avail, while remedial operations, such as Dr. Herrington has described, which prevent the entrance of bile and duodenal contents into the gastric remnant, will not only relieve these distressing symptoms, but will also result in an improvement in the endoscopic appearance of the gastric mucosa.

It is the gastroscopists who have described how commonly one finds bile and duodenal contents in the postoperative stomach; and yet, as has been pointed out, even in the presence of obvious gastritis, comparatively few patients exhibit the classical symptoms. How do these miserable people differ from their asymptomatic fellows?

In the authors' series there is an overwhelming preponderance of reflux gastritis following Billroth II reconstruction, and I wonder if this represents an indictment of the procedure, or was this simply because more of their patients were hooked up this way?

Our own limited experience with patients in whom operation has been necessary would bear out the authors' observation that, in general, a Roux-en-Y diversion is simpler and safer than interposition of a Henle loop; this is particularly true after a Billroth II reconstruction, where you only need to disconnect the afferent limb and attach it to its efferent companion. I would question the need for establishing a defunctionalized limb two-thirds of a yard in length, as some people have advocated, and I must confess that I had never thought of offering either of these operations to a patient who had not undergone previous gastric surgery.

Drs. Herrington, Whitehead, and Sawyers are certainly to be commended for reminding us that reflux gastritis may be responsible for the distress which certain patients experience following operations on the stomach, and for pointing out that such symptoms, when they do occur, are highly characteristic, objectively documentable and surgically remediable, should conservative measures fail to afford relief.

Dr. Marshall K. Bartlett (Boston): What we now call reflux gastritis has been called by various names over the years. The commonest was "afferent loop syndrome," it being thought that bile and pancreatic juice pooled in a dilated and perhaps partially obstructed afferent loop then dumped into the stomach producing pain with relief by vomiting of a considerable volume of bilious material. Since this was often brought on by food, caloric intake was decreased, and weight loss was very frequently of a substantial amount.

We got interested in this subject about the same time Dr. Herrington and his coworkers did, and in 1968 we reported our experience with a small series of five patients. The symptoms our patients had were very much like what you have heard in this series. I think it's interesting that the onset of these symptoms may be anywhere from a few days or weeks after the operation to many years; and why that spread occurs, I haven't the slightest idea.

Even in that early experience we had it was quite evident that it was not necessary to have an afferent loop, because it occurred after pyloroplasty and after Billroth I anastomoses.

In none of the patients we have operated on has there been any evidence of dilatation or obstruction of the afferent loop, in those where there was an afferent loop present. We have used the Roux-en-Y technique. It was reported by Dr. Norman Tanner with considerable success, and so we have simply followed his instructions. We do put the point of inflow of duodenal contents down 50 cm below the gastrojejunostomy. That was reinforced by one of our early patients who had the operation done elsewhere, and it had been put in 25 cm down, and no relief occurred. We moved it down another 25 and he was cured. So we think there's something mystic about something in the range of 50 cm.

This is quite a simple procedure to do, as you have heard from Dr. Herrington, and so we have continued to use it since then.

As far as I know, we have not had a single stomal ulcer, which is perhaps a little surprising. I judge Dr. Herrington has not had any either. Perhaps he would comment on that specific point.

Why it is that with all the patients who have bile and pancreatic juice refluxing into their stomachs after operation, only a few get reflux gastritis remains a total mystery.

Dr. William S. McCune (Washington, D. C.): Our work has been done largely by Dr. Joseph and Dr. Geelhoed. We do not have as many cases as Dr. Herrington.

We agree with the authors that the chief symptoms are bilious vomiting, epigastric pain and discomfort, nausea, and weight loss. Also, I think it is worth mentioning, as he did in his paper, that some blood in the stools is fairly common, and that, of course, there are changes which can be recognized by gastroscopy. I think it's very important to carry out gastroscopy in all these cases; and also to perform an upper g. i. series. The purpose of the gastroscopy is not only to make the diagnosis, but to rule out stomal ulceration.

(Slide) We have a total of 15 patients who have been operated upon for this complication. The types of procedures which were followed by reflux gastritis are as follows. Six of them were Billroth I anastomoses after hemigastrectomy; five followed a Billroth II procedure, and four followed a pyloropasty.

We have occasionally tried to treat these people by use of cholestyramine, and have had some success with it; but these patients are very miserable. I think usually, once the diagnosis is made, if they have been followed for a reasonable length of time, some surgical intervention is needed.

(Slide) We have done two of the repairs by the Tanner procedure, in which the afferent loop is divided, and both ends are put into efferent loop. This has been successful in the two cases in which it was carried out. In all these patients it's necessary to evaluate what surgery has been done previously, and to fit the cure to the original type of operation.

If the patient has not had a vagotomy, he should have one with the secondary procedure.

We have used the interposition of a jejunal loop twice, but in both cases it was unsuccessful, and therefore it had to be taken down. In the others we have performed a roux-en-Y type anastomosis, and in the two cases in which had used an unsuccessful jejunal loop, we took them down and also did a Roux-en-Y. I think 40 cm is a little short; I think 50 cm is better.

These patients must be followed carefully, because of the possible danger of stomal ulceration. We have had no serious hemorrhage in any of our cases, but we have had positive guaiac stools.

Dr. John Ervin Jesseph (Indianapolis): I have been an enthusiastic converter of B. II's to B. I's, and we seem to have a sizable reservoir left in the Midwest. I think part of the reason we're finding them more and more is that our gastroenterologic friends are so vigorous in the use of the flexible scope. They are finding for us, in addition to gastritis, a sizable number of patients with esophagitis, which probably correlates with many of these patients' symptoms, and while such esophagitis does not appear to reach the magnitude it does with peptic reflux esophagitis, it seems to account for considerable symptoms in some patients.

I'm also persuaded, largely by Dr. Herrington's experience and evidence, as well as my own, that this kind of conversion, using one or the other of these forms of interposition, is preferable to a straight gastroduodenal conversion for the symptomatic patient with the Billroth II. Further, I think we ought to remind ourselves that the occasional patient will have no symptoms, but some rather severe process, including a massive hemorrhage from this rather odd form of alkaline gastritis.

Dr. Theodore Drapanas (New Orleans): We have also had a rather large reservoir of patients with gastric surgery at Charity Hospital in New Orleans over the last 25 years, from which we have now culled 30 patients with documented evidence of reflux gastritis which has required surgery.

(Slide) In the paper we gave last year at this meeting we presented our experience with the first 24 patients. You can see that our results are identical with those just presented to you by Dr. Herrington. We agree that the procedure of choice is not the Henle loop, because of its difficulty, but either the Roux-en-Y bypass technique or the Tanner technique. The latter is even simpler than the standard Roux-en-Y.

Now, how did these patients fare? This slide shows our end results, and as you can see, they are excellent.

(Slide) We think it's most important to document, not only by pH studies and by gastroscopy but also by biopsy, the evidence of gastritis. And here is where I believe we differ a bit with Dr. Herrington.

In most of our patients we are able to correlate the degree of symptoms (weight loss, bilious vomiting, and pain) with the degree of gastritis. In our experience, if one begins looking at patients who have diffuse mucosal involvement including edema, inflammation and ulceration of the mucosa, as shown in this particular patient ten years after a Billroth II reconstruction, we think you will be better able to offer procedures to the patients who really need it. This patient did extremely well; in fact, became asymptomatic almost before he went home.

(Slide) We have followed our patients with serial gastric biopsies to document their symptomatic improvement.

(Slide) Here is another biopsy from the same patient, now at five years after a Roux-en-Y reconstruction. The mucosa is normal and he remains asymptomatic and has gained fifty pounds.

Our major point of disagreement with Dr. Herrington is related to the fact that we don't feel that a Roux Y loop longer than 25 cm is needed, and we have not had any regrets for having used 25 cm.

I will close with a question to Dr. Herrington, one that has been asked of me repeatedly by our gastroenterologists. If the results are so good using the Roux-en-Y, and with the use of vagotomy to prevent marginal ulceration, why not offer this as a primary procedure in patients who have had gastric surgery to prevent the development of gastritis?

Dr. Lucius Davis Hill (Seattle): (Slide) This was a patient who had had a gastrectomy, leaving only the antrum, for a lymphoma of the stomach. He did well for a year, and then developed severe bile reflux, with gastritis and esophagitis, approximately two years after surgery.

Lynwood being the authority on this, we called him and asked what he would do with this, and proposed a Roux-Y at the mid-portion of the duodenum. There was some concern about the blood supply here, because of the pyloroplasty at this point, knocking out some of the right gastric blood supply.

We went ahead and did this procedure, after discussing it with him, dividing the duodenum midway between the pyloroplasty and the ampulla and doing a Roux-Y, and I'm happy to say this patient has been completely relieved of the bile reflux. He's only been followed a short period of time, but it's been a gratifying result. We're grateful for Dr. Herrington's consultation.

In a small group of patients we have also utilized a technique of a long jejunojejunostomy in the patient who has a very small reservoir, and wondered about his experience with this. We believe that in these patients the long jejunojejunostomy deviates the bile, perhaps not quite as well as the Roux-Y procedure, but it does, at least in the four patients in whom we have utilized it over the last two years, give the patient an additional gastric reservoir.

Dr. Edward Roy Woodward (Gainesville, Florida): Since the opening of the University of Florida Hospital in 1958 we have done surgical revision on 93 patients because of bile vomiting. Over these intervening years, with the very striking improvement in fiberoptic gastroscopy, along with markedly increased clinical awareness, we feel we can separate today quite accurately those patients who have the mechanical type of afferent loop syndrome and those who have the alkaline reflux gastritis presented by Dr. Herrington and his colleagues.

The differentiation is important, because the mechanical form can be treated very readily by any procedure which does away with the afferent loop. We agree with the authors, however, that duodenal diversion is essential for treating significant symptomatic reflux alkaline gastritis.

We reported a few weeks ago on eight recent patients treated by a duodenal diversion, in whom six months later there was complete gross and microscopic healing of the gastric mucosa. This is a diffuse process, with various mixtures of inflammation, atrophy, and metaplasia, and all three processes are completely reversible.

Our experience corresponds with the authors' in that the syndrome most commonly occurs after Billroth II gastrectomies, but is not uncommon after Billroth I's, and is rather unusual after pyloroplasty. We have had the same favorable results with both the Henley loop and the Roux-en-Y. However, we have seen persistence or recurrence of reflux gastritis in three patients with the Henley loop. So despite the theoretical advantage of routing the ingested food through the duodenal loop, we feel that the Roux-en-Y is the preferable procedure in these patients. All three of these patients were reoperated upon and were cured by the more extensive diversion of duodenal secretions by the Roux-en-Y procedures.

We would re-emphasize again the need for vagotomy plus antrectomy, since the gastric mucosa recovers its ability to secrete acid gastric juice. We would like to emphasize also our observation of the frequent coexistence of reflux alkaline esophagitis. In the eight patients recently reported, six had severe esophagitis. This is possibly related to the diminished gastrin which occurs in Billroth II antrectomy, with a diminished tonus in the lower esophageal sphincter. In these patients the response to duodenal diversion has been equally as effective as in the alkaline gastritis cases.

The term "alkaline" is a misnomer in that none of us believes that bicarbonate is toxic or injurious; it just indicates our ignorance as to which component or components in the duodenal content cause the injury.

Dr. John L. Sawyers (Closing discussion): Certain questions have been raised, one about the length of the Roux limb. I would remind you that the President of this Association, Dr. H. William Scott, Jr. in 1953 reported experimental work in the dog to find the ideal length of a Roux limb to prevent reflux. This length is 45 cm. We have used Roux limbs of this length with good results.

Dr. Drapanas asked if a Roux-en-Y jejunal limb should be used as a primary procedure for patients undergoing gastric resection for duodenal ulcer. Dr. DuPlessis, from South Africa, has been doing this, and we are following his experience with interest.

The question for which we have no answer, but for which many studies have been done in experimental animals with some confusing and conflicting results, is why do some patients have gastritis from bile reflux while other individuals with reflux are asymptomatic with normal gastric mucosa. What sensitizes the patient's gastric mucosa to bile and pancreatic secretions?

It is gratifying that surgeons have effective remedial operations for patients who are incapacitated by bile reflux. We would emphasize the need for accurate diagnosis by gastroscopy and gastric mucosal biopsy. Only these patients in whom the diagnosis of reflux gastritis is documented by gastroscopy findings should remedial operation be performed.

Gastric Mucosal Energy Metabolism and "Stress Ulceration"

RENE MENGUY, M.D., Y. F. MASTERS, B.S.

Acute gastric erosions following hemorrhagic shock (stress ulceration) have been attributed to gastric hyperacidity, altered gastric secretion of mucus and an abnormal permeability of the gastric mucosa to H^+. This report aims at presenting evidence supporting an alternate hypothesis: the event linking shock-induced gastric mucosal ischemia to mucosal necrosis is a deficit in gastric mucosal energy metabolism. Our experimental procedure consisted of harvesting the stomachs of rats and rabbits by "stop-freeze" (liquid N_2) at different intervals after the induction of hemorrhagic shock. Levels of adenosine-phosphates and of glycolytic intermediates in gastric *mucosa* were measured. We studied the changes in the levels of these substrates produced by shock as well as by factors capable, *when combined with shock*, of rendering the gastric mucosa more vulnerable to stress ulceration. The influence of shock and of these modifying factors were evaluated by comparison with data from appropriately designed control experiments. In parallel experiments we examined the frequency of stress ulceration (gross and microscopic) under these same standard conditions. There have emerged from these studies a number of observations all based upon data with the highest statistical significance. The data are consonant with the hypothesis stated above: an energy deficit severe enough to cause cellular necrosis is the event linking shock-induced gastric mucosal ischemia and stress ulceration.

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IN MAN, severe stress in the form of a operation[9] (particularly when complicated by hemorrhage)[14] trauma or thermal burns is sometimes followed by the development of "stress ulcers." It has been noted that the incidence of "stress ulceration" is greater when these situations are complicated by sepsis and/or pulmonary insufficiency.[27] Although the terms "stress ulcer" and "stress ulceration" have become widely used, it should be noted that the lesions usually consist of multiple, superficial *gastric* mucosal erosions rarely extending beyond the muscularis mucosae. Characteristically, these lesions tend to cluster in the mucosa of the corpus and the fundus and respect the antrum.[10,14,26,28] In severe cases the process of mucosal necrosis may extend to the small intestine and colon. Lesions similar in all respects to those observed in patients under the circumstances described above, can be induced by hemorrhagic shock in several animal species and serve as a convenient animal model for the study of this phenomenon. It has also been found that hemorrhagic gastric erosions develop in rodents subjected to physical restraint; lesions to which the term of "stress ulcer" has also been applied.[4,13,24] Although there is no evidence for or against the view that mucosal lesions precipitated by shock have a different etiology from those caused by restraint, we prefer to reserve the term of "restraint ulcers" for the latter and would caution against applying any experimental data derived from the study of this phenomenon to the explanation of the former and vice versa.

The nature of the event or events linking shock or trauma with gastric erosions remains unknown. Stress-induced gastric hyperacidity has been invoked but (except in some instances of cranial injury) has never been substantiated by the demonstration of a consistent pattern of hyperacidity in association with trauma or burns.[16,22,27] On the contrary, the available data indicate that in man as well as in animals, trauma and shock reduce basal gastric acid output.

Others have invoked an alteration in the quantity and the biochemical composition of gastric mucus on the basis of studies showing that ACTH[7] and cortisone[20] reduce gastric mucous secretion. However, this theory

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suffers from a lack of information concerning the possible mechanisms, if any, by which mucus might "protect" the underlying epithelium. It has also been postulated that stress-induced gastric mucosal injury might result from a reduction in the rate of renewal of the surface epithelial layer, a change which might be expected to affect adversely the integrity of the gastric epithelium. This theory was derived from experimental data showing a reduction in the cell turnover rate in the gastric epithelium of animals receiving ACTH or cortisone.[18] Although these changes may play a role in the phenomenon of stress ulceration, we do not believe that they constitute the initial event leading to epithelial breakdown.

In recent years considerable attention has been focused on the possibility that stress-induced mucosal injury may result from back-diffusion of acid through a mucosal membrane rendered more permeable to hydrogen ion by some factor or factors, such as ischemia, associated with the stressful event.[15] Having gained access to the mucosal tissue, hydrogen ion would trigger a chain of events, prominent among which would be hemorrhage leading to focal mucosal necrosis. This theory is based upon the studies of Skillman *et al.*[27–29] who found an increased back-diffusion of acid in the stomach of rabbits 3 hours after the induction of hemorrhagic shock. They made similar observations in critically ill patients and postulated that the gastric hypoacidity often found under these conditions may result from a loss of acid via back-diffusion rather than from an absolute decrease in gastric secretory activity. This line of inquiry was inspired by the classical studies of Davenport[5] on the gastric mucosal barrier. Others[21] have been unable to demonstrate acid back-diffusion in shocked animals.

The studies forming the basis for this report were undertaken to evaluate the validity of an alternate explanation for stress ulceration: *stress-induced gastric mucosal injury results from a mucosal energy deficit severe enough to cause cellular necrosis.* To test this hypothesis we have carried out a series of experiments designed to find evidence to reject it. Our data will show that we have been unable to reject this theory.

I. Is Experimental Stress Ulceration Associated with a Significant Gastric Mucosal Energy Deficit?

Because shock can be expected to produce an energy deficit in most tissues of the body, the hypothesis under study would be tenable only if such a deficit were peculiarly severe in the gastric mucosa.

Materials and Methods

In this first phase of our studies we designed an animal model of shock-induced stress ulceration and examined both the time-course of anatomic gastric mucosal injury and the time-course of changes in gastric mucosal energy metabolism produced by hemorrhagic shock and compared the latter changes with those taking place in other tissues of the same animal.

a) Hemorrhagic shock was induced in 300 g rats by removing 20.0 ml/kg of blood from the vena cava in 2 minutes under light urethane anesthesia. Exactly 15, 30, 45 or 60 minutes later the stomach was removed and studied for erosions and hemorrhage prior to fixation in 10% formalin. Sections from the glandular mucosa were stained with H&E and examined under light microscopy. Eight rats were used for each time interval. Stomachs removed from 6 non-bled rats subjected to 60 minutes of urethane anesthesia served as controls.

b) Rats were subjected to hypovolemic shock as described in the previous paragraph. Exactly 15, 30, 45 or 60 minutes after bleeding, the experiment was terminated by cooling to the temperature of liquid nitrogen, the stomach and wafer-thin slices of liver and skeletal muscle. Identical tissue sampling was done in non-bled rats subjected to the same intervals of light urethane anesthesia. Rats were assigned randomly to the different test and control groups. Levels of ATP, ADP and AMP, of creatine-P (muscle only), glucose-6-P, pyruvate and lactate and glycogen in gastric glandular *mucosa,* and in liver and skeletal muscle tissue (rectus abdominis) were estimated according to standard[1] methods.

Results

a) Gross. The glandular mucosa of stomachs removed 15 or 30 minutes after bleeding appeared normal. Half of the stomachs removed at 45 minutes and all of those examined at 60 minutes showed multiple hemorrhagic foci in the glandular mucosa of the corpus (not in the antrum).

Microscopic. Changes consisting of focal, superficial epithelial necrosis were present in all of the stomachs removed 15 minutes after bleeding (Fig. 1). At 60 minutes these changes had progressed to focal mucosal hemorrhage and superficial erosions (Fig. 2) in all of the stomachs.

b) Changes in levels of adenine nucleotides taking place in gastric mucosa and liver under the influence of hypovolemic shock (approximate 30% reduction in blood volume) are summarized in Fig. 3. In gastric mucosa a 75% drop in ATP levels and a 47% drop in total adenosine phosphates occurred within 15 minutes. Changes in hepatic tissue were significantly less severe and recovery was more rapid. In muscle, a slight but significant drop in levels of phosphocreatine was the only manifestation of enery deficit. In addition, we noted that glycogen levels, normally very low in gastric mucosal

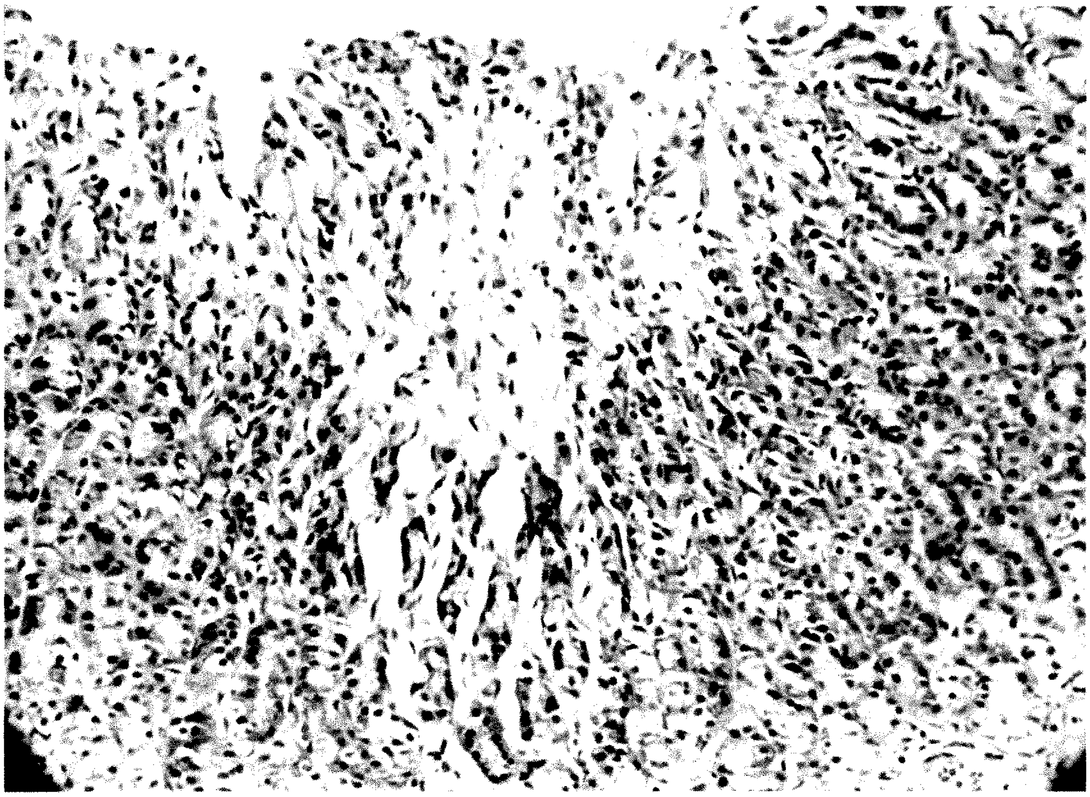

FIG. 1. Section from fundic mucosa of a rat shocked by removal of blood (20.0 ml/kg). Fifteen minutes later the stomach was removed and fixed in 10% formalin. Note the presence of focal mucosal necrosis. (H&E, approx. ×200)

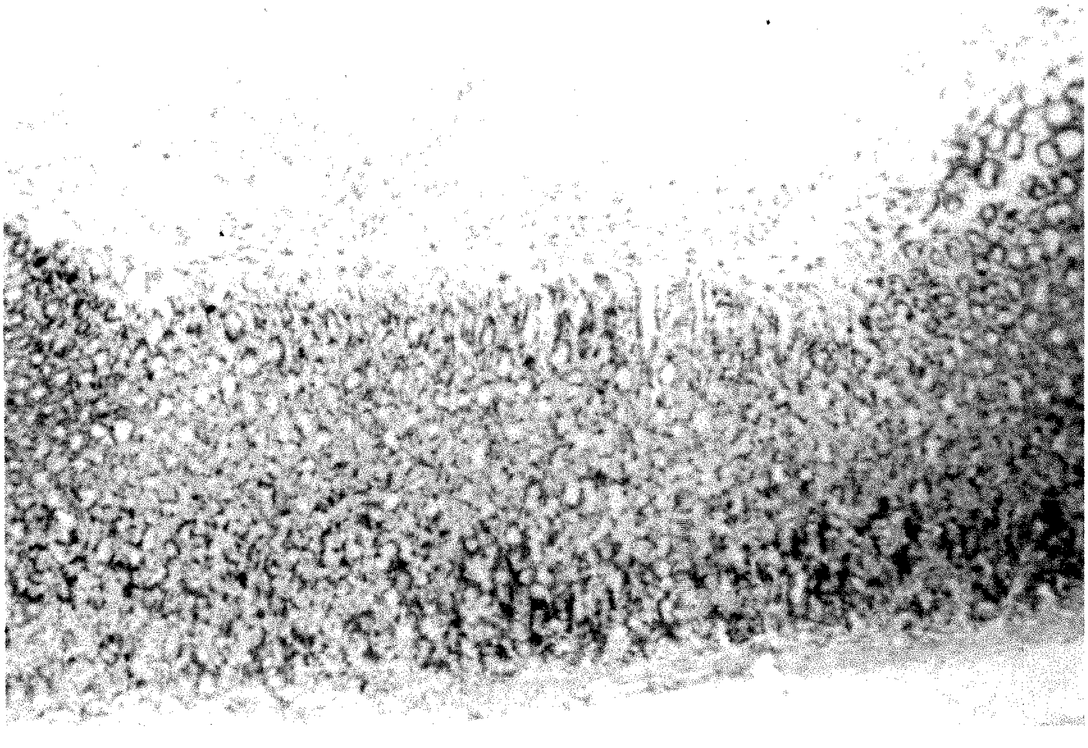

FIG. 2. Section from fundic mucosa of a rat stomach removed 60 minutes after induction of hemorrhagic shock. Section taken through one of multiple mucosal erosions. Note the extensive, superficial mucosal necrosis. (H&E, approx. ×25)

tissue, were almost completely depleted after 15 minutes of shock. Liver glycogen was less severely affected and muscle glycogen remained unchanged. Increases in[lactate]/[pyruvate] were significantly less marked in gastric mucosa than in liver or muscle.

Comment

The energy deficit observed in gastric mucosal and hepatic tissues of shocked rats may be attributed to ischemia and reduced oxidative phosphorylation. The greater severity of the energy deficit in mucosa by comparison with liver and muscle could result from a more severe regional ischemia in this tissue or from a greater vulnerability of gastric mucosal energy metabolism to ischemia. The following experiment was designed to answer this question.

II. Is Gastric Mucosal Energy Metabolism Peculiarly Vulnerable to Ischemia?

We believed an answer to this question might be provided by subjecting gastric mucosa, liver and muscle tissue to identical periods of *complete* ischemia which, by converting these tissues into closed systems and eliminating the factor of differences in input of oxygen and substrates, would limit energy-generating metabolic sequences to the tissue's intrinsic metabolic equipment.

Materials and Methods

Gastric mucosal, hepatic and skeletal muscle tissues were rendered completely ischemic in the following fashion. A silk ligature was placed around the esophagus immediately above the stomach. At the appropriate moment the stomach was lifted from its bed by traction on the ligature and was swiftly and completely severed from all its connections. It was then left *in situ* for 30 or 60 seconds and then frozen to the temperature of liquid N_2. Wedges of liver and rectus abdominis muscle were excised with a single sweep of a scalpel, left *in situ* for 30 or 60 seconds and similarly frozen. Frozen, nonischemic tissues served as controls. Only one tissue sample was taken from an individual animal and this was done in random order.

Results

Changes in tissue levels of adenine nucleotides during complete ischemia are summarized in Fig. 4. After 60 seconds of ischemia the drop in ATP and rise in AMP were significantly greater in gastric mucosa than in hepatic tissue. Levels in skeletal muscle did not change. In addition, we noted at 60 seconds a 60% depletion of gastric mucosal glycogen by contrast with a 16% drop in hepatic tissue and no change in muscle. [Lactate]/[pyruvate] increased significantly only in liver and muscle.

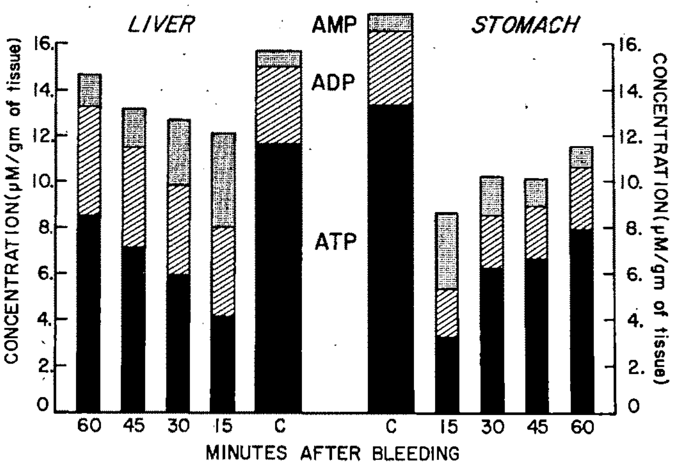

FIG. 3. Influence of hemorrhagic shock on adenosine phosphate levels in gastric mucosa and liver of rats. Bars represent absolute, mean levels (micromoles/gram of tissue, dry weight) of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP). C = control experiments (9). There were 8 experiments at each time interval. All test ATP levels differ ($p < .001$) from control values; changes in [ATP + ADP + AMP] levels in mucosa and liver (−47% and −22%, −38% and −19%, −39% and −16%, −31% and −7% at 15, 30, 45 and 60 minutes respectively) also differ significantly ($p < .001$).

Comment

The data indicate that gastric mucosal energy metabolism is peculiarly vulnerable to ischemia and that the appearance of shock-induced gastric mucosal injury is accompanied by a marked mucosal energy deficit. Although these observations agree with the hypothesis un-

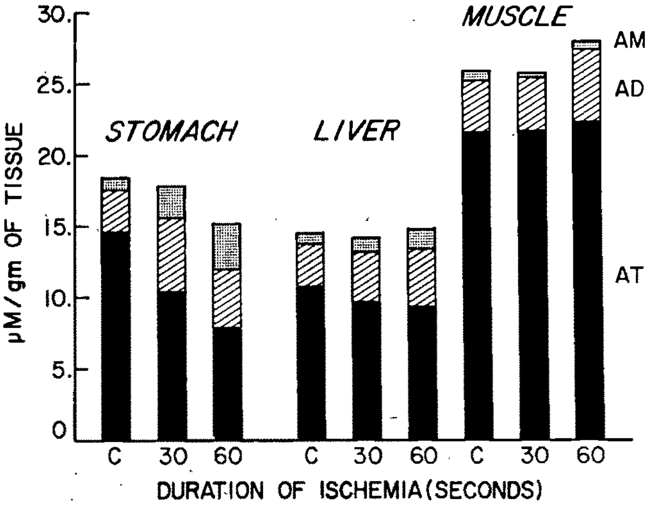

FIG. 4. Influence of *complete* ischemia on adenosine phosphate levels in gastric mucosa, liver and muscle of rats. Bars represent absolute, mean (of eight experiments for each tissue) levels of ATP, ADP and AMP. Changes in these levels in mucosa were significantly different ($p < .001$) from control values (c) at 30 and 60 secs but not in liver and muscle.

der study and do not allow us to reject the theory, they do *not* prove it because we do not know what minimal tissue levels of ATP are essential for cellular survival. Clearly, further experimental testing of the hypothesis is needed. To this end we used an interesting feature of stress ulceration, i.e., the tendency of this phenomenon to involve mainly the corpus and fundus and respect the mucosa of the antum.[10,14,26,28] We reasoned that if the energy deficit developing in the antral mucosa of shocked animals were identical to, or greater, than that taking place in fundic or corpus mucosa, the energy-deficit hypothesis of stress ulceration would not be tenable.

III. Is the Energy Metabolism of Antral Mucosa More or less Vulnerable to Shock Than That of Corpus or Fundic Mucosa?

Materials and Methods

a) Male albino rabbits were maintained on rabbit chow until 6:00 PM of the evening before the experiment when their food was removed and their drinking water was replaced with 500 ml of a 5% sucrose solution. At 8:00 AM the following morning the nutrient solution was removed and the experiment was started at 10:00 AM. Animals were anesthetized with nembutal (30 mg/kg). Artificial ventilation was maintained with room air via tracheostomy. A femoral artery was cannulated and heparin (10 mg/kg) was administered. The plastic arterial cannula was connected via a disposable plastic stop-cock to a pressure transducer and arterial blood pressure was recorded continuously. Hemorrhagic shock was induced by withdrawing, over a period of 5 minutes, an amount of blood sufficient to lower the arterial blood pressure to a mean level of 30 mm Hg where it was maintained by withdrawing appropriate volumes of blood. After 15 or 30 minutes of hypotension, the entire stomach was crushed between 2 large aluminum paddles pre-cooled to the temperature of liquid N_2. Tissue extruding beyond the paddles was severed and the entire sample was dropped into liquid N_2. The entire sample was then lyophilized. Samples of *antral*, *corpus* and *fundic* mucosa were then subjected to the same analytical procedures as described above. Values obtained from tissues of non-shocked rabbits subjected to the same surgical manipulations and 30 minutes of anesthesia served as controls.

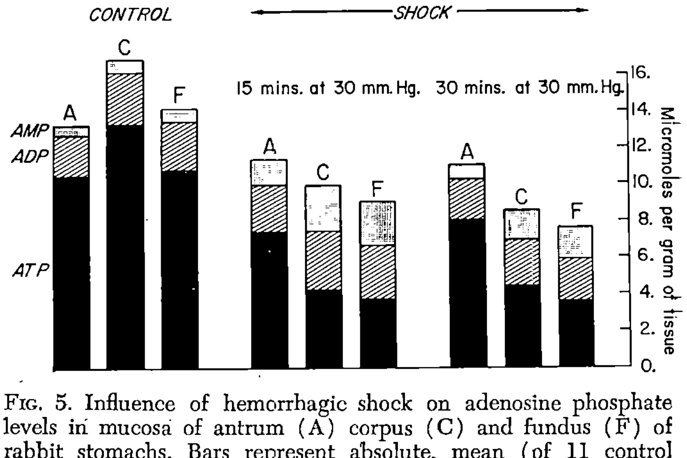

FIG. 5. Influence of hemorrhagic shock on adenosine phosphate levels in mucosa of antrum (A) corpus (C) and fundus (F) of rabbit stomachs. Bars represent absolute, mean (of 11 control experiments and 8 test experiments at 15 and 30 minutes after bleeding) levels of ATP, ADP and AMP. Both at 15 and at 30 mins. after bleeding, ATP levels in antral mucosa were significantly higher than in corpus and fundic mucosae ($p < .01$).

b) Rabbits were prepared for the experiment as in the previous paragraph with the omission of arterial cannulation, heparinization and bleeding. At a given moment (always the same with respect to the induction of anesthesia) the stomach was completely severed from all of its connections. It was left *in situ* for 60, 120 or 180 seconds and cooled to the temperature of liquid N_2. Controls were obtained by freezing the stomach without a preliminary period of ischemia. Frozen stomachs were lyophilized. Dry tissues were opened and samples of antral, corpus and fundic mucosa were taken for biochemical analysis.

Results

a) The data are summarized in Fig. 5. They show that levels of ATP, normally significantly lower in the antral mucosa than in corpus mucosa, remained significantly higher than in corpus and fundic mucosa during up to 30 minutes of hemorrhagic hypotension. An analysis of the data provided by changes in levels of free glucose, glucose-6-P, lactate and pyruvate in these 3 regions of the gastric mucosa during hemorrhagic shock indicated that the more rapid breakdown of high-energy phosphate in corpus and fundic mucosa during shock was accompanied by an accelerated glycolytic flux.

b) Data provided by experiments in which the entire stomach of rabbits was subjected to complete warm ischemia lasting up to 180 seconds showed that dephosphorylation of adenosine phosphates occurred at a twofold *greater rate* in corpus and fundus mucosa by comparison with antral mucosa. As with the shock experiments, the more rapid breakdown of high-energy phosphates in the mucosa of the fundus and corpus was accompanied by a marked acceleration of glyoclytic flux by comparison with antral mucosa.

Comment

These experiments show that a greater energy deficit occurs in the mucosa of the corpus and fundus during hemorrhagic shock. Since stress ulceration produced by experimental shock characteristically affects these regions of the gastric mucosa, the data are consonant with the hypothesis under study, i.e., that shock-induced gastric mucosal necrosis results from a profound mucosal energy deficit. Our data also suggest that the more rapid breakdown of adenosine phosphates in corpus and fundic mucosa during shock does *not* result from regional ischemia (more marked for corpus and fundus than for antrum) since the same differences between antral mucosa on one hand and corpus and fundic mucosa on the other, were found in the mucosa of stomachs subjected to complete ischemia.

In these experiments the animals were *not* fasted and received supplemental carbohydrate before the experiment. Under these conditions the more rapid breakdown of high-energy phosphates in the mucosa of the corpus and fundus was accompanied by an accelerated glycolytic flux, event which suggested that the inability of these regions of the gastric mucosa to maintain the same energy levels as the antral mucosa during shock (or complete ischemia) was *not* due to less efficient anaerobic glycolysis in the parietal cell mucosa but to greater energy requirements in this area of the mucosa. This led us to theorize that the energy deficit in the parietal cell mucosa might be increased by reducing the amount of substrate available for anaerobic glycolysis. If the hypothesis under study is correct and if other conditions (severity of hypotension) remain equal, this greater energy deficit should be accompanied by an increased incidence of stress ulceration. These questions formed the basis for another series of experiments.

IV. Is an Increased Gastric Mucosal Energy Dificit Accompanied by an Increased Incidence of Stress Ulceration?

Materials and Methods

Rabbits were subjected to hemorrhagic shock according to the procedure described in paragraph (a) of Materials and Methods in the preceding series of experiments. After 15 minutes of hypotension the stomach was frozen in situ or the shed blood was returned to the animal and the stomach removed 3 hours later for evaluation of the severity of stress ulceration. These experiments were performed in 2 groups of test animals: 1) rabbits fasted for 24 hours prior to the experiment; 2) and rabbits fed as usual until 6:00 PM of the evening preceding the experiment when their food was removed and replaced by a 5% sucrose solution. Test data were compared with pooled values obtained from fasted and non-fasted rabbits subjected to the same procedure with the exception of bleeding.

Results

a) Influence of Fasting on Shock-induced Changes in Gastric Mucosal Energy Metabolism. Gastric mucosal energy deficit as estimated by a reduction in tissue levels of ATP and of ATP + ADP + AMP was significantly more severe in all regions of the gastric mucosa of the fasted animals. Average percentage changes in ATP levels from control values of antral, corpus and fundic mucosa of non-fasted and fasted animals were -31% and -62% ($p < .01$), -69% and -86% ($p < .001$), -65% and 83% ($p < .05$) respectively. Corresponding values for ATP + ADP + AMP were -14% and -40% ($p < .001$), -41% and -64% ($p < .01$), -36% and -56% ($p < .05$).

In parallel studies we found that the marked hyperglycemia occurring in the non-fasted and shocked rabbits was absent in the fasted animals subjected to the same degree of hemorrhagic shock. Moreover, blood lactate levels were significantly less elevated in the latter than in the former.

b) Influence of Fasting on the Incidence of Stress Ulceration. The data are summarized in Table 1. None of the non-fasted rabbits had gross erosions and only one had mild microscopic evidence of mucosal injury. All but one of the fasted rabbits had very severe erosive, hemorrhagic gastritis in the corpus and fundic mucosa (no antral lesions) when the stomach was examined 3 hours after a 15-minute period of hypotension.

Comment

If we had found that a more rapid breakdown of high-energy phosphate in gastric mucosa was not accompanied by a higher incidence of stress ulceration, the hypothesis under study would not be tenable. Our findings, which show that a greater mucosal energy deficit is accompanied by more severe mucosal injury, are consonant with the hypothesis but do not, of course, prove its validity. Because anaerobic glycolysis present during hemorrhagic shock requires glucose as energy substrate, it is reasonable to assume that the lower blood lactate levels and the absence of hyperglycemia in the fasted rabbits was caused by a rapid depletion of inadequate carbohydrate reserves. The reduced glycolytic flux should impair the capacity of tissues, particularly those with low glycogen levels such as the gastric mucosa, to generate ATP during ischemia. These findings are in agreement with the interesting experiments of Bounous *et al.*[2] who showed that ischemic necrosis of the intestinal mucosa could be prevented by introduc-

TABLE 1. *Incidence of Stress Ulceration*
(Rabbit, 3 hrs. after 15 mins. of Shock)

Control		Fast	
Gross	Micro	Gross	Micro
0/6	1/6	5/6	6/6

ing carbohydrate substrate into the lumen of the intestine.

In pursuing this line of investigation, the thought occurred to us that the energy-deficit hypothesis would be strengthened if it could be shown that an agency, known to render the gastric mucosa more vulnerable to stress ulceration, has an adverse effect on gastric mucosal energy metabolism. We elected to study the action of bile acids whose role in this phenomenon is particularly important since they are naturally occurring substances.

V. Do Bile Salts Reduce the Efficiency of Gastric Mucosal Energy Metabolism?

Several studies have shown that when bile or bile salts are in the lumen of the stomach during hemorrhagic shock, the incidence of stress ulceration is increased.[3,6,12,26] Conversely, stress ulceration in shocked animals is prevented by prior ligation of the common bile duct or of the pylorus.[3,11] Because gastric reflux of bile in man is a well-documented phenomenon which has been incriminated in the pathogenesis of chronic gastric disease, these interesting observations suggest that bile salts may play an important role in the pathogenesis of stress ulceration in man.

Materials and Methods

a) *In vivo* experiments were carried out in rabbits according to the procedure described in paragraph III with the following modifications. Prior to the induction of shock, the pylorus was ligated and the stomach was lavaged with warm 0.9% NaCl until returned fluid was clear. Then 50.0 ml of a solution (H^+,80mEq/l; NA^+, 50 mEq/l; K^+, 10 mEq/l; Cl^-, 140 mEq/l) with or without Na Taurocholate (30 mM) was instilled into the stomach. Twenty minutes later hemorrhagic shock to a level of 30 mm Hg was induced as described previously. Fifteen minutes later the stomach was frozen and fundic and corpus mucosa was subjected to biochemical analysis. (The antral mucosa was not studied in this experiment.) Control animals were subjected to the same procedure but were not bled.

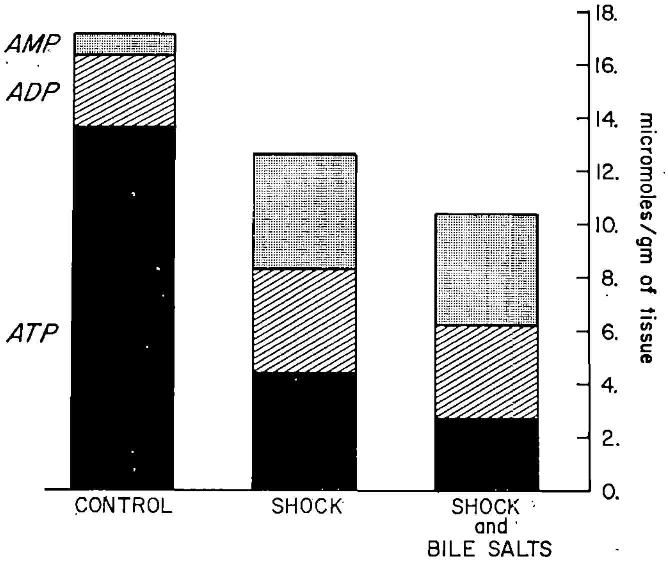

Fig. 6. Influence of Na Taurocholate on oxidation of succinate by mitochondria from corpus mucosa of rabbit stomach. Rabbit liver mitochondria (M) were diluted with an isotonic buffer containing mannitol (45 mM), sucrose (15 mM), EDTA (.02 mM) KCl (40 mM), $MgCl_2$–$6H_2O$ (20 mM), K–PO_4 buffer (20 mM) pH 7.4. Succinate (S) and ADP were added as indicated on the graphs to give final concentrations of 15 mM and .30 mM respectively. Na Taurocholate (B.S.) was added to give final concentrations indicated on the figure.

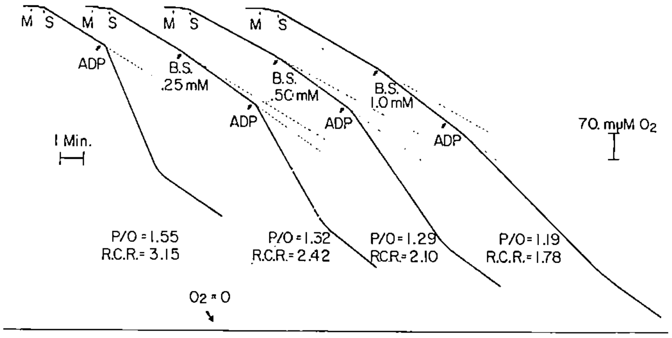

Fig. 7. Influence of bile salts on gastric mucosal energy deficit produced by a 15 min period of hemorrhagic hypotension (30 mm Hg). Bars represent absolute, mean (of 8 control experiments; of 9 test experiments without instillation of Na Taurocholate into the stomach; of 12 test experiments with inragastric instillation of Na Taurocholate at concentration of 30 mM) levels of ATP, ADP and AMP in corpus mucosa of rabbit stomach. ATP levels were significantly ($p < .01$) lower when intragastric instillation of bile salts was superimposed upon shock.

b) The influence of Na Taurocholate on oxidative phosphorylation in vitro was studied with the Clark Oxygen electrode[8] on mitochondria obtained from rabbit corpus mucosa.

c) ($Na^+ + K^+$) –ATPase activity in homogenates prepared from rabbit gastric corpus mucosa was assayed according to standard methods[23] and the influence of different concentrations of Taurocholate on enzyme activity was studied.

Results

a) The data provided by *in vivo* experiments with rabbits are summarized in part in Fig. 6. Average ATP levels in corpus mucosa after 15 minutes of shock were 2.745 μM/g and 4.403 μM/g in the presence and absence of bile salts in the gastric lumen respectively. Corresponding values for fundic mucosa were 2.597 and 4.253. These values differ significantly from each other ($p < .01$ and $p < .01$) as well as from the average control level ($p < .001$).

b) The influence of different concentrations of Na Taurocholate on mitochondrial oxidation of succinate is illustrated in Fig. 7. At low concentrations (.250 mM–1.0 mM) Taurocholate had the characteristic effects of an uncoupler of oxidative phosphorylation: increased state IV respiration and reduced P:O ratio and respiratory control ratio.

c) As can be seen from Fig. 8, Taurocholate in a concentration of 8.0 mM completely inhibited (Na$^+$ + K$^+$)-ATPase activity of homogenates of corpus mucosa (rabbit).

Comment

Our data clearly indicate that Taurocholate has an adverse effect on gastric mucosal energy metabolism. When this bile acid is in the gastric lumen during a short period of hemorrhagic shock, the energy deficit measured in the parietal cell mucosa is greater than when shock is induced in the absence of bile salts from the stomach. This may be explained by the uncoupling effect of Taurocholate on oxidative phosphorylation which we found and which can be expected to reduce the efficiency of respiratory-chain synthesis of ATP. Moreover, the severity of the energy deficit occurring in the gastric mucosa of shocked rabbits in the presence of bile salt may be even greater than the low levels of ATP would indicate since we found that Taurocholate has the added characteristic of inhibiting gastric mucosal (Na$^+$ + K$^+$)-ATPase, i.e. the utilization of ATP.

Discussion

Although none of the experimental data described in this report has provided any evidence that would lead us to reject the hypothesis under study, it should also be made clear that they cannot be accepted as proof of its validity. Because we do not know what are the minimal levels of ATP required for maintenance of cellular integrity *in vivo,* we cannot draw any conclusions regarding the possible impact upon gastric mucosal cellular function of the energy deficits of the magnitude described in this report. We can only *intuitively* postulate that there must be some critically low level of intracellular energy reserves at which the ion pump mechanism should fail with intra-cellular shifts of Na$^+$ and H_2O. There *must* be a critically low level of cellular energy where anaerobic glycolysis is arrested at the phosphofructokinase step for want of ATP. And so on! But until one is able to correlate certain vital cellular functions with ATP levels (or better yet, turnover) the energy-deficit hypothesis of shock-induced tissue injury must remain conjectural.

The assumption that impaired tissue energy metabolism may play a role in some of the manifestations of shock has been examined experimentally beginning with the pioneering work of McShan.[19] Some studies have suffered from the incorrect (we believe) experimental design of attempting to correlate energy deficits in one tissue, such as the liver, with the severity of the general shock syndrome as estimated by animal survival. For instance, the fact that Rosenbaum *et al.*[25] found no correlation between hepatic energy deficits and survival of shocked dogs has been used as an argument against the thesis that such deficits play an important role in the events leading to shock-related death. It may be more rewarding to attempt, as we have, to find an association between one type of shock-induced tissue injury and that tissue's peculiar ability to adjust to the altered environment brought about by the rheologic and metabolic derangements associated with hypovolemic shock.

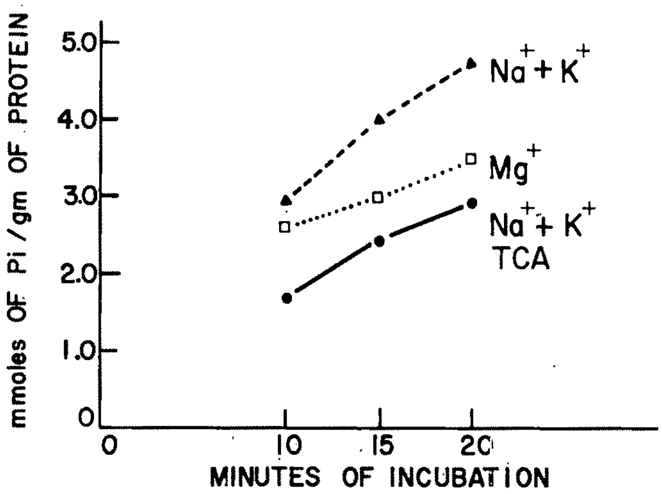

FIG. 8. Influence of Taurocholate (TCA) on adenosine triphosphatase activity (ATPase) of homogenate of rabbit gastric mucosa (corpus). Initial concentrations were 3 mM ATP (Tris salt), 5 mM $MgCl_2$, 100 mM NaCl, (when appropriate), 30 mM KCl (when appropriate), 30 mM Tris (pH 7.4), 8.0 mM Taurocholate (Tris salt) and 0.1 ml of mucosal homogenate in 1.0 ml reaction volume. Reaction was terminated by bringing the mixture to .5M $HClO_4$.

Summary

Shock-induced acute gastric mucosal lesions (stress ulceration) have been attributed to several factors including gastric hyperacidity, impaired gastric secretion of mucus and an abnormal gastric mucosal permeability to hydrogen ion. The purpose of this report is to present evidence for the theory that a deficit in gastric mucosal energy metabolism may be the event linking shock-induced gastric mucosal ischemia to mucosal necrosis. Levels of adenosine-phosphates and of intermediates of glycolysis were measured in the gastric mucosa of rats and rabbits under different experimental conditions. The salient findings were as follows: 1) The appearance of shock-induced gastric mucosal lesions coincides with a severe mucosal energy deficit. 2) Antral mucosal energy metabolism is less affected by ischemia than that of parietal cell mucosa. This results, not from a more ef-

ficient anaerobic energy metabolism in antral mucosa, but from lower energy requirements in this tissue. This observation may explain why stress ulceration characteristically spares the antrum. 3) When the availability of glucose substrate to the gastric mucosa is reduced by a preliminary period of fasting, both the severity of the gastric mucosal energy deficit and the incidence of stress ulceration in response to a standard state of shock increase markedly. 4) We found that Taurocholate has an uncoupling effect on oxydative phosphorylation of mitochondria obtained from the gastric mucosa. Moreover, we found that when Taurocholate is in the gastric lumen during shock, the measured mucosal energy deficit is significantly greater than that produced by the same degree of shock alone. We also found that Taurocholate, *in vitro*, inhibits $(Na^+ + K^+)$-ATPase activity of gastric mucosal homogenate. These observations could explain the well-documented fact that the presence of bile salts in the stomach during shock renders the mucosa more vulnerable to stress ulceration.

These observations are consonant with the hypothesis linking shock-induced acute gastric mucosal necrosis to a severe mucosal energy deficit.

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DISCUSSION

DR. ALEXANDER J. WALT (Detroit): I would like to relate the clinical story of a patient who was admitted to hospital, dehydrated, deeply jaundiced and weak with a pulse of 140, and who was given 7½ L of fluid over the first 24 hours, operated upon the next day, and had a stone removed from the common duct. Four days later, the patient was nauseous and began to vomit. On the ninth postoperative day, he vomited a large amount of blood. On the twelfth postoperative day, the patient passed a red stool and, on the sixteenth day, he died. At autopsy, there were extensive hemorrhages in the mucosa of the stomach and of the colon; no ulceration was present. The year was 1922, and the patient was William Stewart Halsted.

Dr. Halsted seems to have died of erosions of the stomach and of the colon. Now, that's the sort of patient we see in our hospital in Detroit, where from about 1968 until fairly recently we have been treating two patients each week with acute erosive gastritis—so-called stress ulceration—based either on shock or following sepsis. This frequent problem led us to a number of studies as the stomach to us seems to be a target organ in the human. In fact, these lesions appear to be decubiti of the stomach.

(Slide) This will confirm some of the work that Dr. Menguy referred to in the human stomach. Dr. Sugawa has looked in the stomach of ill patients and painstakingly counted each of the lesions—red erosions, black erosions, oozing white erosions, and frank ulcerations. One can see (indicating) that this lesion progresses distally, affecting the body of the stomach from the esophagus downwards. The antrum is relatively immune.

Dr. Lucas took some biopsies from patients to see if we could get a fix on the human condition, and this reflects some of Dr. Menguy's work; cruder, perhaps. You're looking at a scanning electron microscopic picture here, showing the extremely early lesion in a person with a gastric erosion, precisely in the area to which Dr. Menguy referred in his experimental work.

And here is a transmission electron microscope showing the early change of edema, but intact vessels. When the mucosal damage is more extensive, one begins to see the walls break apart, diapedesis of red cells, and further edema, suggesting that the cellular damage to which he refers is now present.

(Slide) This is a human stomach at autopsy, showing lesions in the esophagus, gross involvement of the body of the stomach, and sparing of the antrum. This has led up to some recent dog experiments, in which we were concerned about energy metabolism; again, in a crude sense. Dr. Carrasquilla took a series of dogs and plasmaphoresed them for a week, kept them recumbent, and inserted a nasogastric tube. We were able to produce this picture; again, the body of the stomach grossly involved with erosive gastritis, the antrum spared.

(Slide) In the next series of dogs, you will note how much the stomach of the depleted dog resembles that of the depleted human. In a further group of dogs—prepared in exactly the same way as those you saw previously except that these had intravenous hyperalimentation and a gastrostomy tube instead of a nasogastric tube—the stomachs are in excellent condition, and do not contain the earlier lesions.

Therefore, I have four questions for Dr. Menguy. Firstly, have you noticed clinically a reduced incidence of acute erosive gastritis—parenthetically, I think that we have—and if so would you care to explore the possible reasons? Second, Are you bothered about the presence of nasogastric tubes in the stomach of depleted patients whose energy metabolism may be impaired? Thirdly, would you think that intravenous hyperalimentation, given early, would be worthwhile in people who are at risk?

Dr. Frank G. Moody (Salt Lake City): Dr. Menguy has provided a very attractice hypothesis and an array of data that would tend to support it. However, the hypothesis will have to stand the test of time and further experimentation and, possibly, alternative interpretation.

Let's take the latter first. For example, the marked reduction in the adenylnucleotides in the fundic mucosa might be related to the fact that parietal cells are still secreting acid during the period of hypotension, thereby utilizing these energy substrates to bring them to a level that would be unexpected as compared, for example, to the liver.

I think this is a good possibility. Dr. Menguy would get out of the trap by saying, "Well, the fed rabbits would probably be secreting more acid." But I would remind you that acid plays a critical role in the occurrence of these erosions. Therefore, the presence of food in the stomach might neutralize the acid, and thereby decrease the incidence of ulcerogenesis, as was seen.

As regards the hypothesis, in our work with exteriorized segments of stomach of dog, we have found that there is a decrease in oxygen consumption, which might be considered to be the functional aspect of adenylnucleotides during hemorrhagic shock, during which, indeed, one does get rather severe erosions. However, if one induces acute gastric erosions with direct intraarterial administration of endotoxin, one observes no change in oxygen consumption, but yet produces erosions.

Now, going a step further, if aspirin is used to create erosions, one observes an increase in oxygen consumption. Therefore, I would ask Dr. Menguy if he has used alternative models to explore his hypothesis.

Dr. George H. A. Clowes, Jr. (Boston): Although the work as yet is not completed in our laboratory, we have devised a mechanism for measuring the blood flow of the liver, the portal vein and, of course, then the hepatic artery. One thing of interest is that the blood flow in the total splanchnic bed is lowered proportionately to the total cardiac output in shock, or in the low-output septic state, but the proportionate flow is much greater in the hepatic artery under these conditions. Therefore, it means that the intestine and the stomach actually are getting less blood supply.

Yesterday I mentioned something about the peripheral metabolism in the septic state. I think the same thing is going on in the whole intestinal mechanism, but the sensitive part of it, as Dr. Menguy has pointed out to you, is the gastric mucosa. I think the last gentleman was quite correct in saying that there is a serious deficit of amino acid mobilized to continue supporting the metabolism of these deprived tissues, and that if one used either the amino acid hydrolysate that my colleague, Dr. George Blackburn, has been advocating or hyperalimentation, one might correct this situation and perhaps maintain the metabolism in this seriously depleted tissue which Dr. Menguy has so beautifully shown you this afternoon.

Dr. Melvin Palliser Osborne (Boston): I would like to ask some questions which many of us here are probably pondering.

First, is acid involved in developing these lesions in patients? It may be a long time before we are sure what the mechanisms are, but it may be tomorrow when you need to decide whether or not alkalinization of the stomach is really the key thing to do.

We have been interested in these lesions, and as many of you know, have produced them in young pigs. They are more susceptible to this than are dogs. I think the use of dogs held back study of stress ulcer for a long time, since in the dog the stomach isn't regularly a shock responsive organ.

In the pigs, the obvious thing to do after producing the erosive bleeding lesions in the upper stomach, following shock and reinfusing blood, was to find out whether limiting acidity alters the pathogenesis of the lesions. As it turned out, in studies done and reported with Dr. Anthony Goodman, it does. It prevents some lesions and makes others much milder.

I think it is critical to know whether alkalinization of the stomach is useful. We are trying an extensive controlled study on this in Boston Hospitals in the various shocked, poisoned, perforated and other patients that we treat, but the answers are hard to come by. I sense from some of Dr. Walt's papers in this field that he agrees almost entirely with Dr. Menguy's analysis of the problem. Perhaps he and I could both say that blood flow is deficient and that this leads to these chemical abnormalities that have been measured.

Even Dr. Davenport and others who have studied back diffusion of acid don't exactly insist that acid causes the bleeding lesions.

Dr. B. Eiseman (Denver): A.T.P. is regenerated at a staggering rate. If there were no regeneration we would use up all our body A.T.P. in three seconds. This suggests that in Rene's stress ulcer model there might be a block in A.T.P. regeneration; perhaps at, or prior to, the level of phosphocreatine synthesis and breakdown.

Dr. Menguy's paper is imaginative and will challenge all of us to prove whether the changes in A.T.P. cause ulceration or are only the result of dying and sloughing cells.

Dr. Larry Norton and Mr. Bob Richardson, a medical student in our laboratories, have performed extensive studies on the blood flow characteristics of piglets, in which we can produce stress ulcer by bleeding to 40% of blood volume. They have demonstrated that there are patchy areas of mucosal ischemia at the very site where Dr. Menguy has shown decreased concentrations of A.T.P. Our findings fit very nicely with yours, Rene, and offer an intriguing explanation for why these superficial mucosal cells, which have such a high metabolic rate, should slough out in response to a varity of stresses and irritants, such as bile.

Dr. Rene Menguy (Closing discussion): There is one thing, I think, that needs to be added to what I have said. I think we must give you at least one reason why the stomach is such a poorly privileged site with respect to the effects of stress.

(Slide) This is, one reason. The stomach has virtually no glycogen, by comparison with the enormous glycogen reserves in the liver and the good glycogen reserves in muscle. So the gastric mucosa depends upon a second-by-second supply of oxygen and glucose substrate.

It is even more underprivileged in this regard than the brain, because, like the brain, it has no glycogen, but it does not have phosphocreatine, which the brain has in good amounts. So I think this in part answers Dr. Eiseman's question.

There are probably two tissues in the body which are particularly sensitive to ischemia; the gastric mucosa and the renal tubule.

As far as a block to regeneration of ATP theoretically there is a block which is reached when ATP levels fall below the point required for the phosphofructokinase step, which is about somewhere in the neighborhood of 1.5 to 2 micromoles per gram of tissue. At this point even anaerobic glycolysis has to cease.

Dr. Walt asked me if I had noticed a reduced incidence of stress ulceration. I have not.

With respect to a nasogastric tube, I have tended to avoid it as much as possible, simply on the basis of anecdotal experience that seems to indicate that the traumatic influence of a nasogastric tube against the damaged mucosa may be liable to propagate the process of erosive gastritis.

Is intravenous hyperalimentation worthwhile? Theoretically, I think it is, and I have been using it, at least in the past year. I have used it in three patients with clinically obvious stress ulceration, with apparent good results, for whatever that means.

Dr. Moody's question regarding the influence of acid—when we talk about an energy deficit, there are several factors that go into the equation. One is the demand for energy of the specific tissue at the time it becomes ischemic, and the other is the ability of the tissue to furnish, or to transduce energy via anaerobic glycolysis; and in this regard tissues are going to vary enormously.

I think it is probable that the gastric mucosa does continue to secrete acid, that probably the sodium pump is involved, and this does consume large amounts of energy. I will remind Dr. Moody that the phenomenon of stress ulceration, although we tend to study it in the stomach, because it's there where it occurs most often, really involves the entire g.i. tract, and in severe cases of stress lesions are found throughout the small bowel and, even, in the colon, even though these areas lack acid secreting potential, as you know.

What about endotoxin? I have not studied it. I think it's an entirely different model. Aspirin—we have studied it. Aspirin, as you know, is a potent uncoupler of oxidative phosphorylation, and we have data which we're writing up to indicate that the mechanism of aspirin-induced injury may be somewhat similar.

And Dr. Osborne asked: Is acid involved? I think it is, in several ways, and one way I have already mentioned, and the other is related to the influence of bile salts. I think bile salts play a role in naturally occurring stress ulceration. Bile salts are absorbed the gastric mucosa if the medium is acid, because of the pK of bile salts. So acidity prevailing in the lumen of the stomach will favor absorption of bile salts through the mucosa, and thereby theoretically potentiate their damaging action on the mucosa.

Ulcer Disease, Metabolic Alkalosis and Hyperparathyroidism:

A Mechanism of Interrelationship?

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In both normal volunteers and in patients with primary hyperparathyroidism, the induction of a metabolic alkalosis by infusion of sodium bicarbonate results in a decrease in serum calcium ion and in an increase of circulating parathyroid hormone concentrations. Bicarbonate infusion may serve in man as a new provocative test for release of parathyroid hormone. Furthermore, we speculate that the metabolic alkalosis which is found at times in patients with the Zollinger-Ellison syndrome and severe peptic ulcer disease may result in parathyroid gland stimulation.

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Hyperparathyroidism and peptic ulcer disease are known to be interrelated. Peptic ulcers occur more frequently in individuals with hyperparathyroidism[17] and conversely the finding of a peptic ulcer may be a clue to the diagnosis of hyperparathyroidism.[4] Wilson[33] has found that 20% of the 677 patients with Zollinger-Ellison (Z.E.) syndrome collected in the Z.E. Tumor Registry also had parathyroid gland abnormalities either clinically or at post mortem examination.

Much recent work has focused on the deleterious effect of hypercalcemia on the peptic ulcer diathesis, whether or not associated with Z.E. syndrome.[2,30] This approach favors the concept that the hypercalcemia of hyperparathyroidism increases circulating gastrin and gastric acid secretion[1,6,20,27,29] and hence may exacerbate existing peptic ulcers or result in the formation of new peptic ulcer disease. This appears valid in many instances.

We have approached this problem from the opposite point of view. Is it not possible that some factor or factors associated with peptic ulcer disease and/or the Zollinger-Ellison syndrome may *result* in the formation of hyperparathyroidism?

Recently in our laboratory[10] and at the Mayo Clinic[26] it has been demonstrated that some patients with the Z.E. syndrome have elevated circulating parathyroid hormone (PTH) concentrations despite low or normal serum calcium concentrations. In two of our Z.E. patients with increased PTH and low-normal serum calcium levels preoperatively, surgical excision of the gastrinomas and correction of the gastric hypersecretory state was followed by a decrease of PTH and a rise of serum calcium, both to normal.[10] This is suggestive that we are dealing with a form of *secondary hyperparathyroidism* in some cases of gastrinomas. If so, hypercalcemic hyperparathyroidism associated with this disease may represent tertiary hyperparathyroidism.

Among several factors which may be responsible for this process is systemic metabolic alkalosis. This state may be found in patients who have the Z.E. syndrome[10] and may occur in duodenal ulcer patients following vomiting, nasogastric suction or the ingestion of soluble antacids.

We have previously demonstrated in sheep that acute metabolic alkalosis results in increased secretion of para-

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TABLE 1. *The Effect of Intravenous Sodium Chloride in Normocalcemic Control Patients*

Name, Age, Sex Infusion		Time Min.	Arterial pH	Serum Calcium mg/100 ml	Serum Ionized Calcium mg/100 ml	Serum Proteins g/100 ml	Serum PTH μl-Eq/ml	Serum Gastrin pg/ml	Comments
S.D., 54y, M									
Basal	1		7.41	8.9	4.8	7.1	70	34	Duodenal ulcer
	2		7.41	—	4.7	6.8	—	—	
NaCl		15	7.42	8.4	5.0	6.8	—	—	
4.3 mEq/kg		30	7.39	8.3	4.7	6.9	—	—	
		45	7.40	8.1	4.7	6.7	80	35	
		60	7.39	7.9	4.5	6.2	—	—	
		75	7.41	7.7	4.8	6.2	—	—	
		90	7.41	7.8	4.6	6.2	75	30	
R.T., 22y, M									
Basal	1		7.38	9.7		7.1	45	44	Normal volunteer
	2		7.40	8.7		7.0	—	—	
NaCl		15	7.36	8.7		6.3	—	—	
3.6 mEq/kg		30	7.35	8.2		6.2	—	—	
		45	7.36	8.5		6.2	45	37	
		60	7.35	8.4		6.1	—	—	
		75	7.36	8.4		6.1	—	—	
		90	7.37	8.4		5.8	65	49	
E.H., 22y, M									
Basal	1		7.38	8.9		6.9	100	40	Normal volunteer
	2		7.39	8.6		6.1	—	—	
NaCl		15	7.37	8.6		6.6	—	—	
4.3 mEq/kg		30	7.36	8.5		6.5	—	—	
		45	7.35	8.2		6.4	105	42	
		60	7.38	8.7		6.4	—	—	
		75	7.36	8.3		6.0	—	—	
		90	7.38	8.1		5.9	125	51	
C.R., 26y, F									
Basal	1		7.40	8.6		6.8	50	47	Gastritis
	2		7.40	8.5		7.2	—	—	
NaCl		15	7.41	8.5		7.2	—	—	
5.8 mEq/kg		30	7.38	8.4		6.9	—	—	
		45	7.39	8.2		6.8	65	42	
		60	7.38	8.2		6.8	—	—	
		75	7.40	8.4		6.9	—	—	
		90	7.41	8.0		6.7	70	35	

thyroid hormone.[11] The present study demonstrates these same findings in man. Thus metabolic alkalosis may be one of the links between severe ulcer disease and hyperparathyroidism.

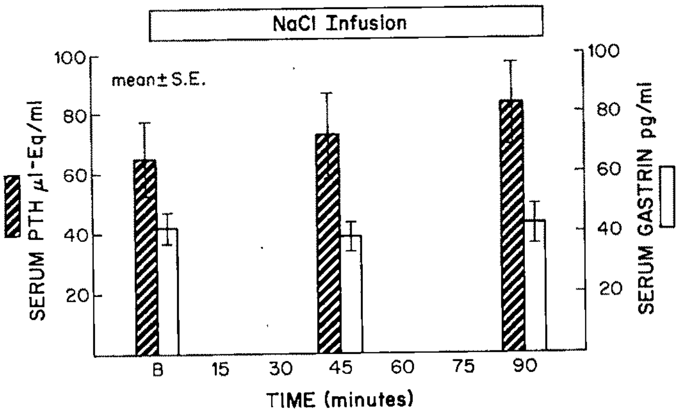

FIG. 1. Infusion of saline into four normocalcemic control patients resulted in no changes in either serum parathyroid hormone (PTH) or gastrin concentrations.

Patients and Methods

Three groups of subjects were studied in the morning hours following an overnight fast.

Control-Saline Group

Four normocalcemic individuals received 580 ml of 3% NaCl (300 mEq) intravenously over a 90-minute period.

Control—Bicarbonate Group

Five normocalcemic individuals received 500 ml of 5% $NaHCO_3$ (300 mEq) intravenously over a 90-minute period.

Hyperparathyroid Bicarbonate Group

Five hypercalcemic patients later proved to have primary hyperparathyroidism also received 500 ml of 5% $NaHCO_3$ (300 mEq) intravenously over a 90-minute period.

Before, during and after the infusions, blood was sam-

TABLE 2. *The Effect of Intravenous Sodium Bicarbonate in Normocalcemic Control Patients*

Name, Age, Sex Infusion		Time Min.	Arterial pH	Serum Calcium mg/100 ml	Serum Ionized Calcium mg/100 ml	Serum Proteins g/100 ml	Serum PTH μl-Eq/ml	Serum Gastrin pg/ml	Gastrin Acid secretion mEq/30 min period			Comments
S.D., 54y, M												
Basal	1		7.39	8.5	4.8	6.3	27	54	Basal	30 min.	3.9	Duodenal ulcer
	2		7.40	—	4.9	6.5	24	—		60	2.8	
$NaHCO_3$		15	7.44	8.3	4.7	6.7	61	56	Infusion	30 min.	2.7	
4.3 mEq/kg		30	7.45	8.0	4.6	6.5	—	—		60	1.6	
		45	7.48	8.0	4.4	6.2	103	—		90	1.1	
		60	7.50	7.9	4.2	6.1	110	66	Post	30 min.	0.1	
		75	7.53	7.7	3.7	6.0	—	—		60	0.1	
		90	7.49	8.0	3.8	5.8	117	50				
R.T., 22y, M												
Basal	1		7.40	9.8		6.4	46	62	Basal	30 min.	1.7	Normal volunteer
	2		7.39	—		6.2	—	—	Infusion	30 min.	2.2	
$NaHCO_3$		15	7.41	9.8		6.2	45	51		60	0.1	
3.6 mEq/kg		30	7.44	9.5		6.1	50	45		90	0	
		45	7.44	9.4		5.9	76	—	Post	30 min.	0	
		60	7.44	9.0		5.6	93	60		60	0	
		75	7.45	8.8		6.3	99	—				
		90	7.47	8.8		6.1	112	56				
E.H., 22y, M												
Basal	1		7.40	10.1		6.8	62	72	Basal	30 min.	2.7	Normal volunteer
	2		7.40	—		6.9	—	—		60	3.8	
$NaHCO_3$		15	7.39	10.0		6.7	64	63	Infusion	30 min.	1.3	
4.3 mEq/kg		30	7.41	9.6		6.6	70	60		60	1.6	
		45	7.41	9.3		6.5	88	—		90	0.6	
		60	7.44	9.0		6.4	120	56	Post	30 min.	0	
		75	7.46	8.6		6.6	137	—		60	0	
		90	7.52	8.3		6.3	180	60				
L.R., 53y, F												
Basal	1		7.45	10.4			21	79	Basal	30 min.	0.2	Gastric ulcer
	2		7.46	10.2			20	—		60	0.2	
$NaHCO_3$		15	7.47	10.0			46	85	Infusion	30 min.	0.1	
3.8 mEq/kg		30	7.51	10.0			52	—		60	0	
		45	7.53	9.8			75	—		90	0	
		60	7.57	9.6			84	64	Post	30 min.	0	
		75	7.58	9.0			99	—		60	0	
		90	7.57	9.0			90	67				
A.H., 23y, M												
Basal	1		7.44	10.2			24	49	Basal	30 min.	0.6	Normal volunteer
	2		7.44	—			—	—		60	0.5	
$NaHCO_3$		15	7.45	10.2			30	—	Infusion	30 min.	0.4	
3.5 mEq/kg		30	7.48	9.8			48	39		60	0.1	
		45	7.50	9.9			52	—		90	0.1	
		60	7.51	9.6			110	41	Post	30	0.5	
		75	7.51	9.4			108	—		60	0.6	
		90	7.50	9.0			121	45				

pled from a radial artery catheter which had been placed percutaneously. Arterial pH, PCO_2, PO_2 and concentrations of blood urea nitrogen, serum Na, K, Cl, CO_2, magnesium, calcium, phosphorus and total proteins were obtained.[11] Serum *ionized* calcium was determined in control patient, S.D., during a saline and bicarbonate infusion utilizing a flow-through electrode system.[16] Gastric acid output (titration to pH 7 with 0.1 N NaOH) was measured in all control-bicarbonate patients.

In addition, all patients had measurement of circulating gastrin and PTH concentrations. Gastrin was measured by radioimmunoassay.[14,22] With this technique, the upper limit of normal for serum gastrin is 120 pg per milliliter.[28] Mean levels for control populations have been reported as 34 ± 4,[13] 71 ± 9[15] and 93 ± 7[21] pg per milliliter. Serum PTH was determined by the radioimmunoassay of Reiss and Canterbury.[23] The serum concentrations of normal subjects by the method used is 10–60 microliter equivalents per milliliter (μl-Eq/ml), an arbitrary unit of measurement relating the potency of the test serum to that of a standard hyperparathyroid serum. The efficacy and reliability of this assay system for the diagnosis of parathyroid gland abnormalities has been clearly demonstrated.[7]

Results

Infusion of 300 mEq of NaCl (3.6–5.8 mEq/kg) into normocalcemic volunteers (Table 1) resulted in no sig-

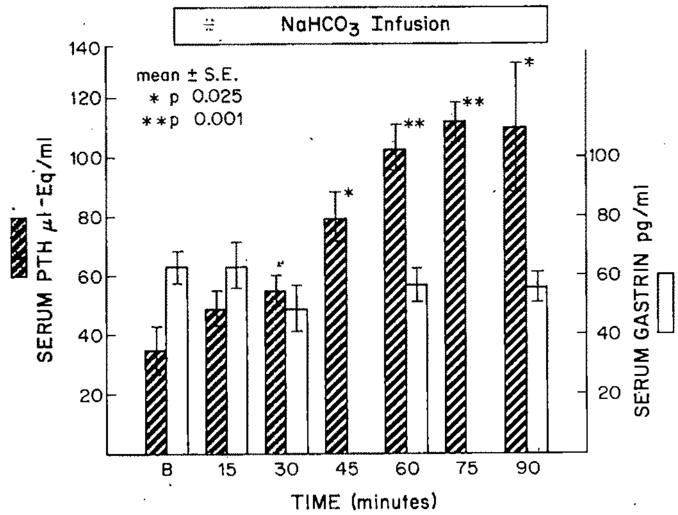

FIG. 2. Infusion of sodium bicarbonate into five control patients resulted in no changes in serum gastrin; however, mean serum PTH concentrations increased to as much as 335% of basal levels.

nificant change in arterial pH although serum sodium and chloride became elevated. Mean serum calcium concentration decreased 0.8 mg/100 ml ($p < 0.025$), however; total serum proteins decreased 0.8 g/100 ml ($p < 0.01$) as well indicating that the fall in total calcium concentration was likely to be dilutional. Serum ionized calcium, on the other hand, did not decrease in patient S.D. in whom it was measured (Fig. 3). In response to saline infusion neither circulating PTH nor gastrin concentrations changed significantly (Fig. 1).

In each control patient who received an infusion of sodium bicarbonate (3.5–4.3 mEq/kg) a typical hypokalemic, hypochloremic metabolic alkalosis developed (Table 2). Arterial pH increased from 0.06 to 0.14 units in these subjects. Mean serum calcium concentration decreased 1.2 mg/100 ml ($p < 0.01$) during this 90-minute period. Total proteins decreased 0.5 g/100 ml; however, this change was not statistically significant. In contrast to the saline infusion, serum ionized calcium in patient S.D. decreased 1.2 mg/100 ml coincident with the development of alkalosis (Fig. 3). Basal serum PTH concentrations were 21 to 62 μl-Eq/ml in this control group. During the bicarbonate infusions circulating PTH increased to values which were 240–500% of basal; the mean PTH concentration increased from 35 μl-Eq/ml (basal) to 112 μl-Eq/ml at 75 minutes, $p < 0.001$, (Fig. 2). Serum gastrin did not change significantly from basal during the bicarbonate infusions, however, gastric acid secretion decreased in 4 of 5 individuals in whom it was studied and remained constant in the fifth.

Among the five individuals who were subsequently found to have proved hyperparathyroidism, four had multiglandular disease and only patient, I.B., appears to have had a single adenoma (Table 3). In response to the bicarbonate infusions in this group, arterial pH increased 0.11 to 0.19 units. Coincident with this change, total calcium concentration decreased in each individual. The maximal mean decrease in serum calcium of 1.4 mg/100 ml, $p < 0.05$, occurred 60 minutes after starting the infusion. Fasting PTH concentrations were 87 to 274 μl-Eq/ml in these patients. During bicarbonate infusions PTH concentrations increased to values which were 130–250% of basal. The mean basal PTH concentration of 170 μl-Eq/ml increased to 289 μl-Eq/ml, $p < 0.05$, 60 minutes after the start of the infusions (Fig. 4). Mean gastrin concentrations were normal in these 5 individuals and did not change during the induction of alkalosis.

Discussion

The possible causes of parathyroid gland abnormalities associated with the Z.E. syndrome are listed in Table 4.

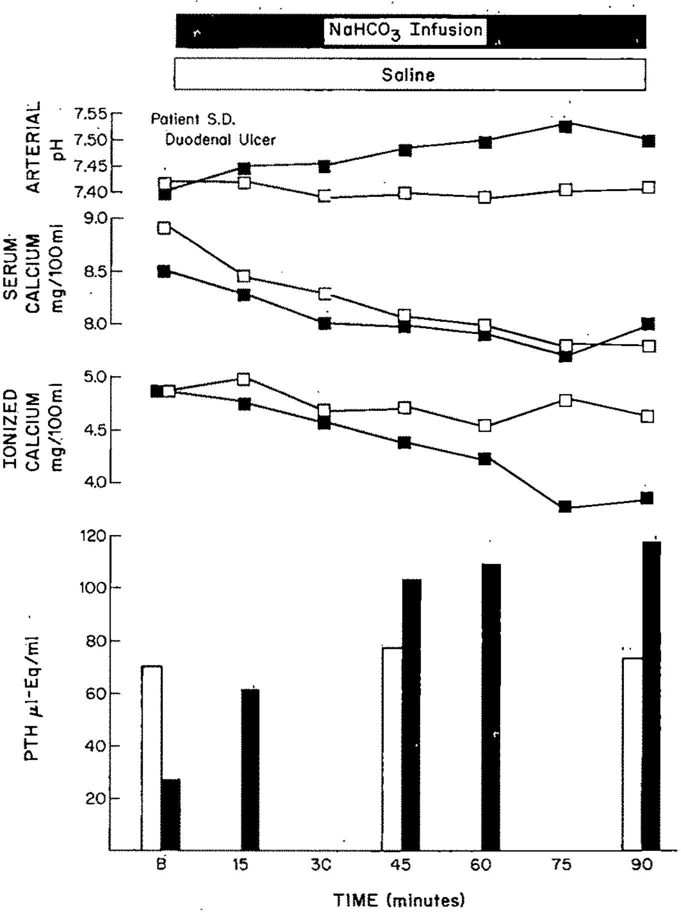

FIG. 3. Importance of calcium ion in regulation of PTH secretion. Patient S.D., was given a saline infusion and an infusion of sodium bicarbonate on separate days. In response to the saline infusion no changes in serum PTH concentrations were noted. However, coincident with the induction of acute metabolic alkalosis (NaHCO$_3$ infusion), serum PTH increased markedly. Note that parathyroid hormone secretion correlated inversely with changes in serum calcium *ion* concentrations.

TABLE 3. *The Effect of Intravenous Sodium Bicarbonate in Patients with Primary Hyperparathyroidism*

Name, Age, Sex Infusion	Time Min.	Arterial pH	Serum Calcium mg/100 ml	Serum PTH μl-Eq/ml	Serum Gastrin pg/ml	Pathologic Findings of Parathyroids
E.C., 32y, F						
Basal 1		7.44	11.6	103	87	L upper—140 mg hyperplastic
2		7.44	—	—	—	L lower biopsy
NaHCO$_3$	15	7.47	11.4	163	—	R upper—100 mg hyperplastic
4 mEq/kg	30	7.49	11.0	225	92	R lower—95 mg hyperplastic
	45	7.52	10.8	—	—	Chief cell hyperplasia
	60	7.53	10.6	240	69	
	75	7.57	10.0	255	—	
	90	7.58	10.0	250	90	
H.M., 48y, F						
Basal 1		7.39	11.1	87		R upper—2015 mg adenoma
2		7.39	10.9	—		R lower—147 mg parathyroid and thymus
NaHCO$_3$	15	7.43	10.5	—		L upper—74 mg hyperplastic
3.1 mEq/kg	30	7.44	10.4	123		L lower biopsy
	45	7.49	10.0	—		
	60	7.49	9.8	126		
	75	7.50	9.9	—		
	90	7.49	9.8	146		
I.B., 42y, F						
Basal 1		7.44	13.5	274	37	Chronic lymphatic leukemia
2		7.44	13.6	248	—	L upper—528 mg chief cells
NaHCO$_3$	15	7.53	12.8	—	37	R lower biopsy—normal
	30	7.59	12.7	250	39	Only two glands were found at surgery. Her clinical
	45	7.59	12.0	323	—	course suggests that this was an adenoma since
	60	7.60	11.7	345	33	she has remained normocalcemic for two years.
	75	7.59	12.0	—	—	
	90	7.63	12.3	356	43	
F.C., 57y, M						
Basal 1		7.38	14.2	150	27	R upper—355 mg adenoma
2		7.37	14.2	174	—	R lower—18 mg normal
NaHCO$_3$	15	7.43	13.5	182	28	L upper biopsy
3.7 mEq/kg	30	7.49	13.2	200	24	L lower—222 mg adenoma
	45	7.52	12.0	358	—	Additional papillary-follicular thyroid cancer was
	60	7.51	11.8	400	25	found and a total thyroidectomy performed
	75	7.51	11.5	—	—	
	90	7.51	12.2	400	30	
H.B., 68y, F						
Basal 1		7.45	11.3	236	10	L upper—2600 mg adenoma
2		7.45	11.3	—	—	L lower—42 mg ? hyperplasia
NaHCO$_3$	15	7.45	11.0	230	33	R upper—50 mg adenoma or hyperplasia
5.2 mEq/kg	30	7.50	10.5	282	34	R lower biopsy
	45	7.50	10.5	297	43	
	60	7.52	10.5	325	47	
	75	7.57	10.5	339	—	
	90	7.58	10.4	336	45	

Most authors have taken the view that the parathyroid changes which occur with gastrinomas are part of an inherited syndrome referred to as Wermer's syndrome or multiple endocrine adenomatosis, type 1.[31] While this may be the case, the finding that individuals with the Z.E. syndrome may have elevated circulating PTH without hypercalcemia[10,26] and in fact may have mild hypocalcemia[10] supports the theory that this process may be *secondary hyperparathyroidism.* Pathologically, the parathyroid glands associated with gastrinomas usually manifest chief cell hyperplasia or multiglandular involvement,[18] findings which support this concept.

The known causes of secondary hyperparathyroidism are chronic renal failure and malabsorption. Renal impairment due to severe dehydration or hypokalemia may occur in Z.E. syndrome due to severe gastric hypersecretion and diarrhea; however, this was not present in the patients with Z.E. tumors and increased PTH secretion cited above.[10] Malabsorption of calcium and/or vitamin D may be expected to occur in some patients with the Z.E. syndrome. Acidification of the upper small intestine due to gastric hypersecretion is known to result in malabsorption of fats in many of these patients.[9] This remains a fruitful area of investigation.

Elevated circulating polypeptide hormones are also known to influence calcium homeostatis. Patients with Z.E. syndrome have been demonstrated to have elevated serum gastrin, glucagon[8] and/or calcitonin.[26] Each of

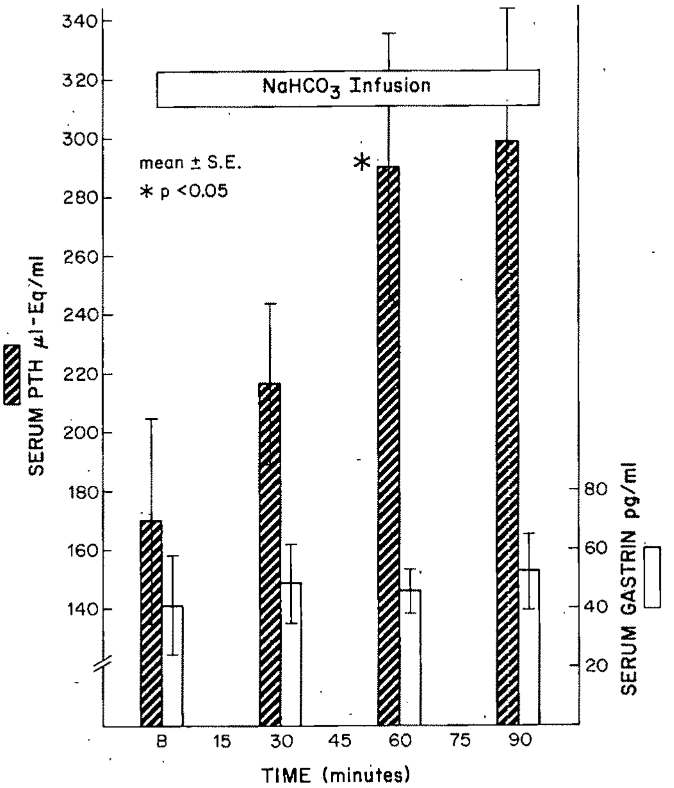

FIG. 4. An infusion of sodium bicarbonate was given to five patients with proved primary hyperparathyroidism. Serum gastrin concentrations did not change. However, concentrations of PTH increased significantly to 170% of basal values at 60 minutes.

these has been reported to lower serum calcium in experimental animals and/or in man.[3,5,19] Whether or not hypersecretion of these polypeptides results in secondary hyperparathyroidism in man remains a very active field of investigation.

The other possible mechanism of secondary hyperparathyroidism, the one that we have examined in the present study, relates to the fact that a systemic metabolic alkalosis may be found in individuals with the Z.E. syndrome.[10] Presumably this is related to the persistent gastric hypersecretion in these patients. Metabolic alkalosis also occurs in duodenal ulcer patients following vomiting, nasogastric suction or ingestion of soluble antacids. We have previously demonstrated in sheep that a sodium bicarbonate infusion and the production of acute metabolic alkalosis results in a decrease of ionized calcium concentration and a coincident elevation of circulating PTH.[11] In the present study similar results were obtained in man. In both normal patients and others with primary hyperparathyroidism, sodium bicarbonate infusion resulted in a consistent elevation of circulating parathyroid hormone.

TABLE 4. *Possible Etiologies of Hyperparathyroidism Associated with the Zollinger-Ellison Syndrome*

1. Genetic—Wermer's Syndrome
2. Secondary to malabsorption of Vitamin D and/or Calcium
3. Secondary to secretion of polypeptides
    - Calcitonin
    - Gastrin
    - Glucagon
4. Secondary to Metabolic Alkalosis

It is well known that the most important stimulant of PTH secretion is a decrease in serum *calcium ion* concentration. In our studies of patient S.D., the exquisite sensitivity and responsiveness of PTH secretion to changes in calcium ion is once more demonstrated (Fig. 3). The importance of pH changes on calcium ion concentration has been well described. Moore[16] has demonstrated *in vitro* that alkalosis lowers and acidosis raises the calcium ion concentration. We have confirmed these findings *in vivo* in sheep.[12] In normal human subjects, Seamonds and associates[25] have shown that the elevation of blood pH associated with hyperventilation and/or the post-feeding state results in a decrease in serum calcium ion with no change in total serum calcium concentration. This post-prandial alkalosis is thought to be the result of gastric acid secretion and has been shown to be exaggerated in duodenal ulcer patients due to gastric hypersecretion of acid.[24] If so, one may speculate that a greater or more prolonged decrease of calcium ion may occur in these patients and thus may result in more intense stimulation of their parathyroid glands.

Finally, in previous experiments in sheep,[12] we found that bicarbonate infusion increased circulating serum gastrin as well as PTH. In man this does not occur. Serum gastrin remained unchanged despite the production of systemic alkalosis. However, during these bicarbonate infusions titratable gastric acidity decreased in the control group.

The importance of our findings in man may be threefold:

1) Sodium bicarbonate infusion appears to be a new, safe and effective provocative agent for release of parathyroid hormone. In healthy individuals it may replace the more dangerous EDTA test in differentiating between parathyroid adenomas and hyperplasia.

2) Wills[32] postulated that parathyroid hormone may play an important role in maintenance of acid-base balance in man. Our data partially confirm this hypothesis. Since it is known that an increase in PTH secretion results in a hyperchloremic, metabolic acidosis, the following sequence may be postulated: Metabolic alkalosis→ ↓ serum (Ca^{++})→ ↑ PTH secretion→ correction of alkalosis.

3) Finally, the cycle of metabolic alkalosis, depressed serum ionized calcium concentration and parathyroid stimulation demonstrated in these experiments may represent a major mechanism in the etiology of parathyroid

disease associated with severe peptic ulcer disease and Z.E. tumors. As in other known causes of secondary hyperplasia, hypercalcemic hyperparathyroidism may later occur and is referred to as tertiary hyperparathyroidism.

Acknowledgments

We are indebted to Barbara J. Hill for her expert assistance, to Dr. Janet Canterbury and Dr. Eric Reiss for their help, to Dr. J. F. Rehfeld for the gift of antigastrin antibody and to Mr. Michael Borish and Mrs. Lorraine Williams for preparing this manuscript.

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DISCUSSION

DR. JAMES CHARLES THOMPSON (Galveston): I question whether there *is* an increased incidence of duodenal ulcer in hyperparathyroidism. I know that it has been quoted as gospel, and I know that Barreras in his massive review article last year, finally, after wrestling with himself for 40 pages, concluded that there was; but the data are certainly not clear. Any time you want to relate one disease to another, you are in difficulty, and when you want to relate a disease as common as peptic ulcer to any other disease, your first question must be: What population is going to serve as a control for the unique thing that I'm trying to prove?

As far as I know, the only condition that has been indisputably proven to have an increased incidence of peptic ulcer is chronic obstructive pulmonary disease.

Now, to get to this paper, in patients with both hyperparathyroidism and Zollinger-Ellison syndrome, we have taken a different tack, a tack that seemed logical to us (and one that Dr. Josef Fischer and his colleagues have taken), namely that we ought to do the simpler operation first; that is, take out the parathyroid adenoma and see what happens to the serum gastrin level.

We have five of these patients. In all of them the serum gastrin level fell. In two of them the serum gastrin has risen slowly to the point that the patients have become quite symptomatic, and we have had to go ahead and take out a Z-E tumor. In the other three, the serum gastrins are beginning to rise, and I suspect that they will turn out to have an autonomous Z-E tumor, but we don't know that yet, and we have followed one of them for, now, three years.

Dr. Kaplan's entire hypothesis rests on three assumptions. Actually, one is proven; the other two, I think, are fairly shaky. The first is that metabolic alkalosis causes an increase in parathormone release. He and his colleagues have demonstrated this previously in sheep, and have shown it elegantly here in these studies in man and in a patient with hyperparathyroidism.

Secondly, it rests on the presumption that the Zollinger-Ellison syndrome and duodenal ulcer are associated with alkalosis. Well, that can only be true if acid is being lost from the body. Now, there is a great deal of acid within the gut in people who have the Zollinger-Ellison syndrome, but after awhile they compensate for that, and, as far as I know, the vast majority of people with the Z-E syndrome who are not vomiting and who are not undergoing nasogastric aspiration, or who don't have some fantastic diarrhea in which they are losing acid through the stool, except in those instances I think they are not alkalotic. Certainly the vast majority of duodenal ulcer patients are not alkalotic, unless they are undergoing nasogastric aspiration or are obstructed.

Thirdly, tertiary hyperparathyroidism can arise from metabolic alkalosis in these patients only if the alkalosis were prolonged. A biologic change of that severity, or that consequence, it seems to me, would require a rather prolonged period of alkalosis in order to generate the changes necessary to promote tertiary hyperparathyroidism.

Now, my question is: Why not first find out if duodenal ulcer patients and Z-E patients *are* alkalotic before we construct all these hypotheses? Why not do a survey? It's hard to get a mass survey of unoperated Z-E patients, but several of the VA hospitals are trying nonoperative treatment (of all heresies) on some of them, and they have, I know, a collection of a few, and we have one or two, and I'm sure that we could get a couple of dozen whom we could measure many times, to see if they are alkalotic, and that would seem to me to be the most important single point.

DR. RICHARD E. WILSON (Boston): The authors are postulating a form of secondary hyperparathyroidism resulting from persistent alkalosis, which has many similarities to the secondary hyperparathyroidism in renal failure patients. It is because of my extensive experience with this problem that I rise to ask some questions.

We have recognized secondary hyperparathyroidism as existing to some degree in all patients with renal failure. Only a mild degree of hyperparathyroidism exists, however, for many months or years in these patients, and this is in the face of truly profound hypocalcemia. Severe hyperplasia develops, so as to produce hypercalcemia, in only a very few of these patients out of the many hundreds we have studied. In all our patients this has only been chief cell hyperplasia—no adenomas—and no patients have tertiary hyperparathyroidism, which I happen to consider a complete misnomer.

I think that the time course of hypocalcemia must be important as a mechanism, and I'd like to ask Dr. Kaplan to tell us of any documentation of significant hypocalcemia, not just low normal serum calciums, in Z-E patients. What is the incidence of chief cell hyperplasia versus adenoma in this patient population? I know that some of these patients have had adenomas. Also what is the length of time of persistent alkalosis which he thinks is required to produce this syndrome?

DR. STANLEY R. FRIESEN (Kansas City, Kansas): I'd like to make three points. One, I think this paper is important, because it demonstrates that there is a delicate homeostasis in the foregut endocrine system. This alkalosis which they have produced through the intravenous infusion of soda bicarb has increased the levels of PTH probably through the mechanism of decreased calcium. Exocrine substances can influence the release of endocrine substances.

Another thing that I would like to bring out is that perhaps we need to know whether alkalosis is frequently seen in duodenal ulcer and Z-E patients. Certainly, secondary hyperparathyroidism is common in these latter patients, and perhaps it can occur independently of the presence of alkalosis and a decrease in calcium. In other words, I think you can get hyperparathyroidism without a measurable decrease in serum calcium as the cause of it.

There is one other point I want to make, that there is a common denominator, probably, in duodenal ulcer patients and patients with hyperparathyroidism. In hypersecretory states including acromegaly there is G-cell hyperplasia of the antrum. This G-cell hyperplasia may represent a work hyperplasia, or a compensatory phenomenon to the acid inhibition which is present in these hypersecretory states. On the other hand, this G-cell hyperplasia as well as the hyperplasia of chief cells in secondary hyperparathyroidism may have basis in a genetic abnormality.

DR. PAUL H. JORDAN, JR. (Houston): It has been suggested that there is a polypeptide in the antrum other than gastrin which causes the release of thyrocalcitonin. I would like to ask Dr. Kaplan if he thinks that as a possible hypothesis release of thyrocalcitonin in some patients is under the influence of the antrum and that in order to compensate for this the parathyroids work overtime and produce either hyperplasia or an adenoma.

We have seen one patient who had his antrum resected for duodenal ulcer. After removal of the antrum, a parathyroid adenoma which had not been evident preoperatively became manifested immediately postoperatively and was removed.

We don't have techniques for measuring thyrocalcitonin, and I just wondered if he has any information on this point.

DR. EDWIN L. KAPLAN (Closing discussion): When a patient is recognized to have a high serum calcium, and parathyroid gland abnormalities are found at surgical exploration, we refer to this state as primary hyperparathyroidism. It is called *primary* because no precipitating cause for this is known. On the other hand, it has been demonstrated that some individuals first have a lower than normal serum calcium (secondary hyperparathyroidism) and with time the serum calcium concentration rises above normal. This process is referred to as *tertiary* hyperparathyroidism and has been documented in chronic renal disease and in malabsorptive states. A question which intrigues us is whether this same process may occur under other circumstances and not be recognized.

The following may be a case in point. It has been clearly demonstrated that in the last trimester of pregnancy the maternal circulating parathyroid hormone (PTH) increases markedly, presumably due to a transfer of calcium to the fetus. Is it not possible that after repeated pregnancies and repeated bouts of stimulation of the parathyroid glands that hypercalcemic hyperparathyroidism may occur. We call this primary hyperparathyroidism. Perhaps it is not primary at all but rather the result of the pregnancies (and therefore tertiary).

In our paper, we present the same hypothesis. At present, when hypercalcemic hyperparathyroidism occurs in patients with the Zollinger-Ellison syndrome this is considered to be part of the syndrome of multiple endocrine adenomatosis, type I (MEA-I) and, therefore, to be the result of heredity. On the other hand we have studied patients with Z.E. syndrome and found some to have increased circulating PTH and low or low-normal serum calcium concentrations suggesting that the parathyroid abnormalities are the result of the low serum calcium.

Of course glucagon, gastrin, or calcitonin secretion or calcium and Vitamin D malabsorption may be responsible for these effects, but in today's paper we have chosen to restrict our comments to the possible role of acid-base changes in the formation of parathyroid hyperplasia. Dr. Thompson is correct in asking whether patients with primary hyperparathyroidism really have an increase in duodenal ulcer disease. I agree with him that these data are not clear. On the other hand it has been definitely demonstrated that an "alkaline tide" or systemic alkalosis occurs in man after eating and that the magnitude of this is directly related to the amount of gastric acid secretion. In patients with the Z.E. syndrome whom we have studied there has sometimes been a metabolic alkalosis and this has been noted by others in the literature as well.

In response to Dr. Wilson's comments, the incidence of hyperplasia or multiglandular parathyroid abnormalities is much higher in the M.E.A. 1 or 2 syndromes and in familial hyperparathyroidism than in the usual case of primary hyperparathyroidism. The serum calcium concentration does not have to change considerably to result in parathyroid gland hyperactivity. We have demonstrated previously that a decrease of calcium ion of less than 0.5 mg % results in a doubling of circulating PTH in man. Thus the serum calcium concentration may remain within the statistical range of normal and still result in parathyroid overactivity in a given individual.

Our speculations concerning the role of metabolic alkalosis in the production of parathyroid disease may be controversial, however there is little question that metabolic alkalosis does result in a decrease in circulating calcium ion and an increase in parathyroid hormone secretion.

The Influence of Total Gastrectomy on Survival in Malignant Zollinger-Ellison Tumors

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JEROME J. DECOSSE, M.D., PH.D., STUART D. WILSON, M.D.

The effect of total gastrectomy on the biologic behavior of malignant gastrinomas was studied from patient data collected in the ZE tumor registry. A total of 267 patients with documented metastatic tumor had definitive gastric operations. In the 137 patients who had total gastrectomy, survival was 75% at one year, 55% at five years and 42% at ten years. In the 130 patients who had lesser gastric operations, survival was 51% at one year, 27% at five years and 18% at ten years. Deaths from progressive tumor growth occurred in 17% of the patients at risk after total gastrectomy and 30% of the patients at risk after lesser gastric operations. A subgroup of 127 patients with documented liver metastasis had definitive gastric operations. Seventy-three patients with liver metastasis had total gastrectomy with survival of 68% at one year, 42% at five years and 30% at ten years. Fifty-four patients with liver metastasis had lesser gastric operations with survival of 44% at one year, 7% at five years and none at ten years. Deaths from progressive tumor growth occurred in 25% of the patients at risk after total gastrectomy and 50% of the patients at risk after lesser gastric operations. Regression of metastatic ZE tumor was clearly documented in only four patients; all had total gastrectomy. Presumptive regression of primary tumor occurred in seven patients, five had total gastrectomy. The study clearly demonstrated that total gastrectomy was the procedure of choice for malignant ZE tumors, even in the presence of widespread metastasis. The results provided indirect evidence to support a gastric feedback effect which influences growth of gastrinomas; however, the results also show that total gastrectomy furnished neither predictable nor permanent protection from subsequent tumor growth and metastasis.

From The Medical College of Wisconsin and Milwaukee County Medical Complex, Milwaukee, Wisconsin

In 1955, Zollinger and Ellison described two patients with marked gastric hypersecretion, peptic ulcer disease resistant to conventional surgical management and associated non-beta islet-cell tumors of the pancreas. They postulated that an "ulcerogenic humoral factor" was responsible for the peptic ulcer diathesis.[24] The ulcerogenic hormone elaborated by these tumors is now known to be gastrin and these tumors may appropriately be called gastrinomas. Complete removal of the target organ for gastrin, the stomach, has been necessary to control the ulcer diathesis in most patients because the gastrin-producing tumors are often multiple or malignant with metastases.[7]

During the past decade, a number of patients with known metastatic islet-cell carcinoma have been reported to survive five and even ten years following total gastrectomy.[10,20,22,23] The inordinately long survival and reports of tumor regression after total gastrectomy suggest that removal of the end organ, the stomach, might influence tumor growth.[5,8,9,11] This study investigates the influence of gastrectomy on survival and death from tumor in patients with proven metastatic islet-cell carcinoma.

Patient Material and Method of Study

Patient data for this study were obtained from the Zollinger-Ellison (ZE) Tumor Registry established in 1962[6] to accumulate patients with proven ZE syndrome in order that the natural history and preferred treatment of this disease could be evaluated. Nearly 800 patients have been collected with adequate information for analysis of tumor pathology, extent of surgery and cause

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of death. No attempt has been made to collect all occurring cases. Original patient data were obtained from personal experience, case reports in the literature, a 1962 survey of university teaching centers, and personal communications with physicians. Followup information was obtained through correspondence with the reporting physicians. Documentary information was programmed for computer analysis and periodically updated.

Only patients with verified metastasis of ZE tumor to lymph nodes, liver, lung or other organs were selected for study. These patients could be assumed to harbor malignant neoplasm which was likely to progress after gastric surgery; their survival might, therefore, reflect tumor growth. Individual variables of this series of patients were analyzed to identify factors which may have contributed to survival. The effect of gastric operation was studied by comparing survival, longevity, and causes of death in those patients treated by total gastrectomy and those patients treated by lesser but definitive gastric operations. Included in the lesser gastric operations were gastroenterostomy, vagotomy and antral drainage, partial gastrectomy with or without vagotomy, and "near total" gastrectomy.

Patients with documented liver metastasis were isolated to represent a subgroup of patients in whom a more consistently aggressive neoplasm was present and in whom differences of survival might be magnified. A comparison was made between the patients treated by total gastrectomy and those managed by lesser gastric operations.

Causes of death were categorized as follows: 1) directly related to complications of ulcer diathesis; 2) directly related to progressive tumor growth or metastasis; 3) directly related to a complication of surgery occurring within 30 days of operation; and 4) deaths from other causes.

Survival was calculated by the actuarial or life-table method[1] without adjustment for age because there were no significant differences in the ages of the groups compared. Survival was calculated from the time of definitive operation.

All patients who demonstrated objective evidence of partial or complete tumor regression were recorded. Objective evidence of tumor regression was defined as disappearance of tumor mass or reduction in size as determined by physical examination, operation, autopsy, or radiologic examination.

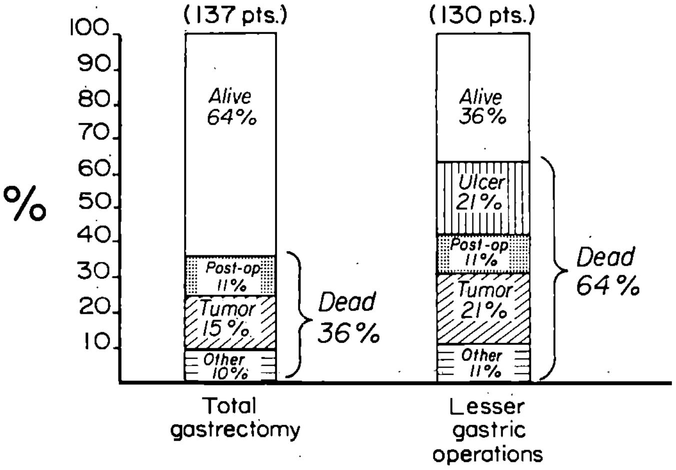

FIG. 1. Cause of death in all Z-E patients with metastasis who had definitive gastric surgery. Tumor deaths did occur in the total gastrectomy group but were less frequent than after lesser gastric operations. A substantial number of patients died from ulcer complications when total gastrectomy was not performed.

Results

ZE Tumor with Proven Metastasis

A total of 267 patients underwent definitive gastric operations and had malignant ZE tumors with proven metastasis. These patients were divided into two groups: 137 patients treated by total gastrectomy and 130 patients treated by lesser gastric operations. The two groups were statistically similar with respect to age, sex, duration of symptoms prior to treatment, number of operations, extent of metastases, and other variables which might influence survival. Crude mortality was 36% after total gastrectomy and 64% after lesser gastric operations (Fig. 1). After total gastrectomy 15% died from progressive tumor growth; 11% died from postoperative complications; and 10% died from other causes. Forty-three per cent of the deaths occurred within 30 days of operation. After lesser gastric operations 21% died from progressive tumor growth; 21% died from complications of the ulcer diathesis; 11% died from postoperative complications; and 11% died from other causes. Forty-one

TABLE 1. *ZE Tumor with Proven Metastasis: Deaths from Progressive Tumor Growth*

Group	Patients	Early Deaths	Patients at Risk	Tumor Deaths No.	 % at Risk	 Mean Survival
Total Gastrectomy	137	18	119	20	17*	41.7 months
Lesser Gastric Operations	130	39	91	27	30*	26.6 months

* $p < 0.05$.

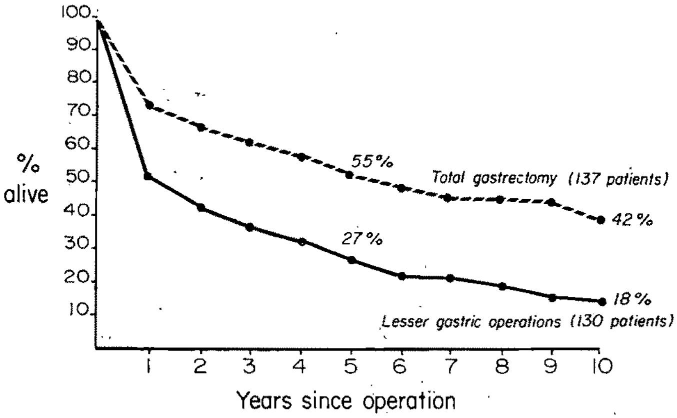

FIG. 2. Survival rates in all Z-E patients with metastasis. Significantly better survival following total gastrectomy was apparent up to ten years.

per cent of the deaths occurred within 30 days of operation.

In this series of patients with metastatic ZE tumor, comparison of tumor death rate for patients at risk yielded significant difference between the two groups (Table 1). After total gastrectomy there were 18 early deaths from postoperative complications leaving 119 patients at risk. Twenty patients, or 17% of those at risk, died from progressive tumor growth with a mean length of survival of 41.7 months (range 1-120 months) after total gastrectomy. After lesser gastric operations there were 15 early deaths from postoperative complications and 24 early deaths from ulcer complications leaving 91 patients at risk. Twenty-seven patients, or 30% of those at risk, died from progressive tumor growth with a mean length of survival of 26.6 months (range 1-120 months) after operation.

The extent of gastric resection significantly influenced survival in patients with metastatic ZE tumor (Fig. 2). After total gastrectomy, actuarial survival was 55% at 5 years and 42% at 10 years. After lesser gastric operations, actuarial survival was 27% at 5 years and 18% at 10 years (Table 2). Median length of life was 5.5 years after total gastrectomy in contrast to 1.2 years after lesser gastric operations.

TABLE 3. *ZE Tumor with Liver Metastases*

Treatment	Patients	Deaths No.	Deaths %
No Definitive Gastric Operation	30	27	90%
Lesser Gastric Operations	54	44	81.5%
Total Gastrectomy	73	33	45.2%
	157	104	66.3%

Late death from tumor progression occurred in 8, or 22%, of the 36 patients with metastatic ZE tumor who lived for five or more years after total gastrectomy. The remaining 28 patients are alive; 14 of them are alive 10 or more years after total gastrectomy.

ZE Tumor with Liver Metastasis

Overall survival was directly proportional to the extent of gastric resection in the subgroup of 157 patients with histologically documented liver metastasis (Table 3).

Thirty patients with liver metastasis had no definitive gastric operation. Eight of these patients had no operation at all but were discovered to have ZE tumors with liver metastasis at autopsy. The remaining 22 patients had operations for either ulcer disease or tumor symptoms but did not have definitive gastric procedures. In some, the diagnosis of ZE syndrome was not recognized until autopsy. In other patients, the extent of tumor prevented the surgeon from attempting major gastric resection. Only three of these patients have lived. One patient was found at operation to have an islet-cell tumor with liver metastasis; he is alive and asymptomatic six months later. The second living patient in this group had marked gastric hypersecretion but no ulcer. Metastatic islet-cell tumor was discovered by liver biopsy. He is alive and receiving chemotherapy one year later. The third patient is alive 11 years after the discovery of a

TABLE 2. *Life Table: ZE Patients with Proven Metastasis*

	Interval (Years)	Alive at Onset (No.)	Died (No.)	Withdrawn (No.)	Accumulative Survival %	Accumulative Survival S.E.
Total Gastrectomy	1	137	31	39	74.6	.040
	2	67	5	14	68.4	.045
	3	48	3	5	63.9	.049
	4	40	2	2	60.6	.052
	5	36	7	14	55.1	.056
	10+	15	1	14	42.0	.069
Lesser Gastric Operations	1	130	58	30	51.5	.046
	2	52	8	9	42.8	.047
	3	35	4	4	37.6	.048
	4	27	3	0	33.5	.049
	5	24	8	10	27.2	.048
	10+	6	2	4	18.1	.050

TABLE 4. *ZE Tumor with Liver Metastasis: Comparison of Patient Groups*

Group	Number	Sex	Mean Age at Onset	Mean Duration of Symptoms to First Operation	Mean Number of Operations	Other Endocrine Disease
Total Gastrectomy	73	1.6 M/F	36.43 years (S.D. 15.71)	2.57 years (S.D. 3.74)	2.68 (S.D. 1.66)	23.3%
Lesser Gastric Operations	54	1.1 M/F	40.97 years (S.D. 14.44)	3.50 years (S.D. 5.24)	2.64 (S.D. 1.43)	29.6%

large pancreatic islet tumor with liver metastasis. This patient received radiation therapy and subsequent palliative resection of tumor but had no definitive gastric surgery.

A total of 127 patients with liver metastasis underwent definitive gastric operations. The group of 73 patients who had total gastrectomy were evenly matched to the group of 54 patients who had lesser gastric operations with respect to age, sex, duration of symptoms, and other variables (Table 4). The crude mortality was 45% after total gastrectomy compared to 81% after lesser gastric operations (Fig. 3). After total gastrectomy 22% died from progressive tumor growth, 11% died from postoperative complications, and 12% died from other causes. Thirty-three per cent of the deaths occurred within 30 days of operation. After lesser gastric operations 33% died from progressive tumor growth, 28% died from ulcer complications, 11% died from postoperative complications and 9% died from other causes. Thirty-six per cent of the deaths occurred within 30 days of operation.

The death rate from progressive tumor growth differed considerably between the two groups when only those patients at risk were compared (Table 5). After total gastrectomy there were nine early deaths from postoperative complications leaving 64 patients at risk. Sixteen patients, or 25% of those at risk, died from progressive tumor growth with a mean survival of 39.3 months (range 1-120 months). After lesser gastric operations there were six early deaths from postoperative complications and 12 early deaths from ulcer complications leaving 36 patients at risk. Eighteen patients, or 50% of those at risk died from progressive tumor growth with a mean survival of 30.3 months (range 1-84 months).

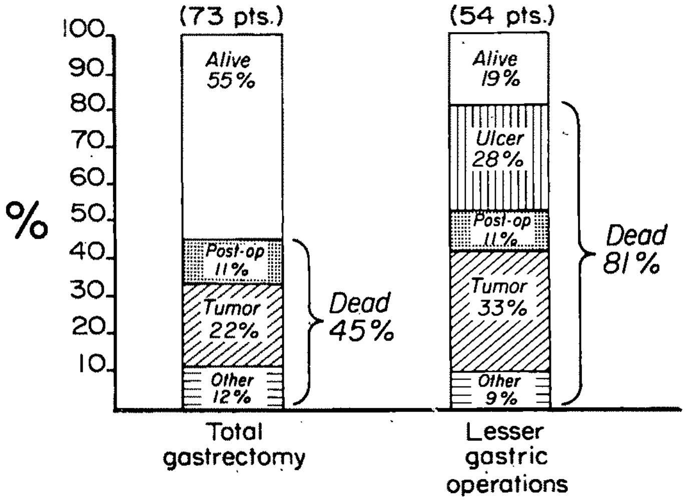

FIG. 3. Cause of death in Z-E patients with liver metastasis who had definitive gastric surgery. Increased mortality following lesser gastric operations can be attributed to death from recurrent ulcer disease and a greater number of deaths from tumor.

Actuarial analysis of survival showed significant differences between total gastrectomy and lesser gastric operations in these patients with liver metastasis (Fig. 4). After total gastrectomy 42.3% of patients could be expected to survive five years and 30.3% could be expected to survive ten years. In contrast, after lesser gastric operations, only 7.3% of patients could be expected to survive five years and no patients could be expected to survive ten years (Table 6). Median length of life was 4.4 years after total gastrectomy in contrast to less than one year after lesser gastric operations.

Late death from progressive tumor growth occurred in six, or 33% of the 18 patients with liver metastasis who survived for five or more years after total gastrectomy. The remaining 12 patients are alive; 8 of them are alive 10 or more years after total gastrectomy.

Tumor Regression

Metastatic ZE tumor objectively regressed in only four patients; all had total gastrectomy (Table 7). Patient No. 313 had tumor regression which was unrelated to the timing of total gastrectomy. Metastatic liver tumor actually progressed for three years following total gastrectomy. The patient then had surgery for cholecystitis and suppurative cholangitis at which time numerous large liver metastases were documented. Following cholecystectomy, the liver metastases regressed such that palpable liver masses disappeared and the radioisotope liver scan became normal. The tumor has remained in regression for nine years although at present the serum gastrin remains elevated.[4]

In the other three patients, regression of metastatic tumor correlated with total gastrectomy. Patients No. 089 and No. 019 are alive but have developed recurrent tumor; both have survived seven years since total gas-

TABLE 5. *ZE Tumor with Liver Metastasis: Deaths from Progressive Tumor Growth*

Group	Patients	Early Deaths	Patients at Risk	Tumor Deaths		
				No.	% at Risk	Mean Survival
Total Gastrectomy	73	9	64	16	25*	39.3 months
Lesser Gastric Operations	54	18	36	18	50*	30.3 months

* $p < 0.05$.

trectomy.[10,15] Patient No. 093 died from recurrent metastases after a 12-year period of tumor regression.[10]

A group of 30 patients had tumor only in lymph nodes without identification of the primary source. Tumor regression was presumed in these patients if after a substantial time of survival subsequent operation, autopsy or gastrin radioimmunoassay failed to reveal evidence of residual or primary tumor.

Fourteen patients, with lymph node tumor only, had lesser gastric operations (Table 8). Six of these patients died, four with continued ulcer diathesis and thus indirect evidence of residual gastrin-producing tumor. Six of the eight surviving patients have only short-term followup. The other two surviving patients are alive 10 and 11 years since operation and have had questionable tumor regressions. One of these patients[17] had both a subtotal gastrectomy and a pancreatico-duodenectomy. There was no evidence of primary tumor in the resected specimen but a microscopic primary focus might conceivably have been removed. The other patient had a parapancreatic tumor documented by biopsy. Subsequently, gastric secretion decreased to normal and the patient was reported as a spontaneous regression.[13] Recurrent ulcer and bleeding has since prompted reoperation at which time no residual tumor was apparent. A vagotomy and pyloroplasty was performed and the patient has remained asymptomatic for 10 years.[12]

Sixteen patients, with lymph node tumor only, had total gastrectomy; twelve have survived for variable periods of followup. Five patients demonstrated presumptive tumor regression after total gastrectomy. Two patients from our medical center illustrate this phenomenon (Figs. 5, 6).

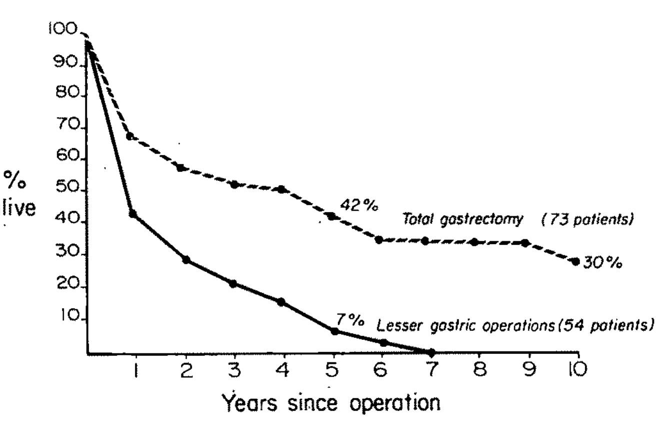

FIG. 4. Survival rate in Z-E patients with liver metastasis. Survival was thirty per cent at ten years after total gastrectomy. No patients survived longer than seven years after lesser gastric operations.

Discussion

Our results showed a significant superiority of total gastrectomy in the treatment of patients with metastatic ZE tumors. Although a formidable procedure, total gastrectomy was warranted even in the presence of liver metastasis and has provided acceptable long-term survival. Improved survival from total gastrectomy in the treatment of patients with gastrinomas was attributed initially to complete removal of all the acid-producing parietal cells and, thus, control of the ulcer diathesis. It soon became apparent that many patients who harbored residual tumor after total gastrectomy survived for remarkably long periods without progression of tumor.[10,20,22] The possible influence of total gastrectomy on growth of tumor was noted and a "feedback" mechanism was suggested.[5,8,9] Based on observations of the absence of residual tumor and metastasis at second-look operations[9] and observations of radiographic disappearance of tumor metastasis, Friesen proposed a "gastric factor" which influenced growth of islet-cell tumors.[8] He postulated a feedback relationship between the stomach and pancreatic tumor whereby the stomach directly or indirectly stimulated tumor growth and production of gastrin. On the basis of this concept, total removal of the stomach would abolish this trophic influence and cause regression or lack of progression in growth of the islet-cell tumor. A more recent "overview" theory implicates the hypothalamus and pituitary gland as possible mediators in the feedback cycle.[11]

Our study indirectly supports the concept of a gastric influence on tumor growth. Lack of tumor progression was common after total gastrectomy but uncommon after operations which spared part or all of the stomach. Tumor deaths were significantly less frequent after total gastrectomy than after lesser gastric operations. Patients who died from progressive tumor growth after total gastrectomy had a longer length of survival than patients who died from progressive tumor growth after lesser gastric operations implying that tumor growth was slower when the stomach was absent. Regression of

TABLE 6. *Life Table: ZE Patients with Liver Metastasis*

	Interval (Years)	Alive at Onset (No.)	Died (No.)	Withdrawn (No.)	Accumulative Survival %	S.E.
Total Gastrectomy	1	73	20	31	68.5	.059
	2	32	4	4	59.3	.067
	3	24	2	2	54.2	.070
	4	20	1	1	51.4	.072
	5	18	5	4	42.3	.076
	10+	9	1	8	30.3	.082
Lesser Gastric Operations	1	54	28	7	44.1	.071
	2	19	6	2	29.4	.068
	3	11	3	0	21.4	.063
	4	8	2	0	16.0	.058
	5	6	4	2	7.3	.043
	10+	0	0	0	0	

metastatic tumor was uncommon but may have been influenced by the absence of stomach, occurring in 4 of the 137 patients with malignant ZE tumors who had total gastrectomy but none of the 130 patients with malignant ZE tumors who had lesser gastric operations.

Regression of primary tumor or regression of tumor in regional lymph nodes was much more difficult to document. Regression of primary tumor was presumed to have occurred in patients who had tumor found only in lymph nodes and who subsequently demonstrated objective evidence that no residual tumor remained. This phenomenon again was more likely to occur in the absence of the stomach. We assume that lymph node tumor in these patients does, indeed, represent metastasis of undetected primary tumor and that subsequent absence of tumor activity is due to regression or at least quiescence of the primary focus. After total gastrectomy, nearly one-third of the patients with lymph node tumor only have shown evidence of this "regression or quiescence" implying that these occult lesions may be more sensitive to the "biologic feedback mechanism."

On the other hand, our results also show that total gastrectomy does not provide permanent control of tumor growth and metastasis in patients with malignan ZE tumors. Only four of 137 patients who had total gastrectomy for malignant tumors had clear-cut, documented tumor regression; three have subsequently developed recurrent tumor and the fourth has a markedl elevated gastrin level suggesting residual tumor. Furthermore, in one of these patients, the regression was no related to the timing of total gastrectomy. With longe followup observation, a growing number of deaths fron tumor were recorded in patients who had total gastrectomy. The observation that progressive tumor deaths ar more frequent in those patients with liver metastasis i in agreement with other recent reports.[2,15,18]

Early reports of tumor regression may have led t undue optimism in the management of malignant gastrinomas. Our results show that a guarded prognosis b applied, particularly to patients with liver metastasis Radioimmunoassay techniques to measure serum gastrin which have been most helpful to the surgeon by providing a definitive preoperative diagnosis, may be used t assess residual tumor activity in the postoperative period

TABLE 7. *Documented Regression of Tumor Metastasis*

Patient	Age at Operation	Sex	Criteria for Regression	Current Status	Comment
Reg. No. 313[3,4]	15	Male	Palpable liver masses and defects on liver scan disappeared.	Alive 12 years since total gastrectomy. Gastrin > 5000 picrogram per ml.	? spontaneous regression. Tumor progressed for three years after total gastrectomy. Regression followed operation for cholecystitis.
Reg. No. 089[8,10]	43	Male	Liver metastases gone at "second look". Lung metastasis on x-ray disappeared.	Alive 7 years since total gastrectomy. Recurrent tumor. Gastrin elevated.	Temporary regression for 6 years.
Reg. No. 019[15]	43	Male	Palpable liver masses disappeared.	Alive 7 years since total gastrectomy. Recurrent tumor in liver.	Temporary regression for 6 years.
Reg. No. 093[8,10]	35	Male	Liver metastases gone at "second look." Mediastinal mass on x-ray disappeared.	Dead from widespread recurrent metastases 13 years after total gastrectomy.	Temporary regression for 12 years.

TABLE 8. *ZE Tumor in Lymph Node Only*

Operation	Patients (No.)	Dead (No.)	Tumor Progression (No.)	Presumptive Regression (No.)
Total Gastrectomy	16	4	1	5
Lesser Gastric Operations	14	6	4	2?

Serial measurements of serum gastrin after total gastrectomy show a persistent hypergastrinemia in most patients with liver metastasis.[16,18] A "normal" serum gastrin level should be interpreted with caution because it does not necessarily imply the absence of residual neoplasm. Some patients with residual gastrin-producing tumor will have a normal fasting gastrin level but will demonstrate a marked rise in serum gastrin after calcium or secretin infusion.[14,16,18] Calcium or secretin presumably stimulates the release of gastrin from islet-cell tumor and thus permits identification of patients with residual neoplasm.

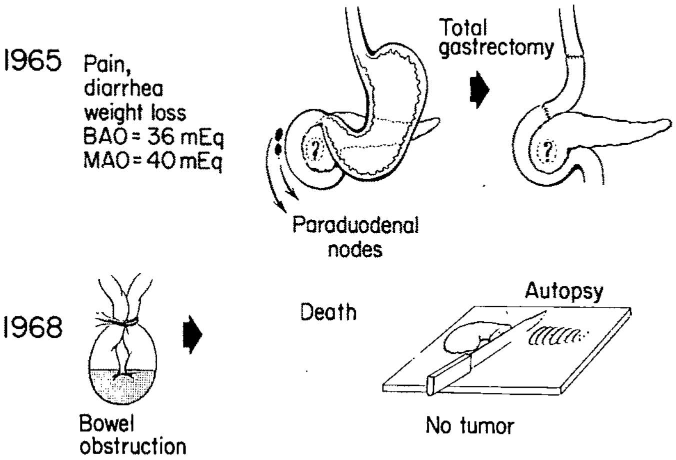

FIG. 5. Reg. No. 325. C. S., a 46-year-old woman who had a four-year history of abdominal pain, weight loss, and diarrhea. Gastric secretory studies suggested Z-E syndrome. At operation in 1966, metastatic islet-cell carcinoma was found in two excised paraduodenal lymph nodes. A small mass of uncertain nature was noted in the head of the pancreas but not biopsied. Total gastrectomy was done. Three years later, the patient unfortunately died from a strangulated intestinal obstruction. At autopsy no residual tumor was found despite a careful search of the pancreas and surrounding areas.

Acknowledgment

We wish to acknowledge Jerry Anderson, from the Biostatistics Section, Medical College of Wisconsin, for the statistical analysis.

We are grateful to the physicians who have provided followup information on their patients to the ZE Tumor Registry.

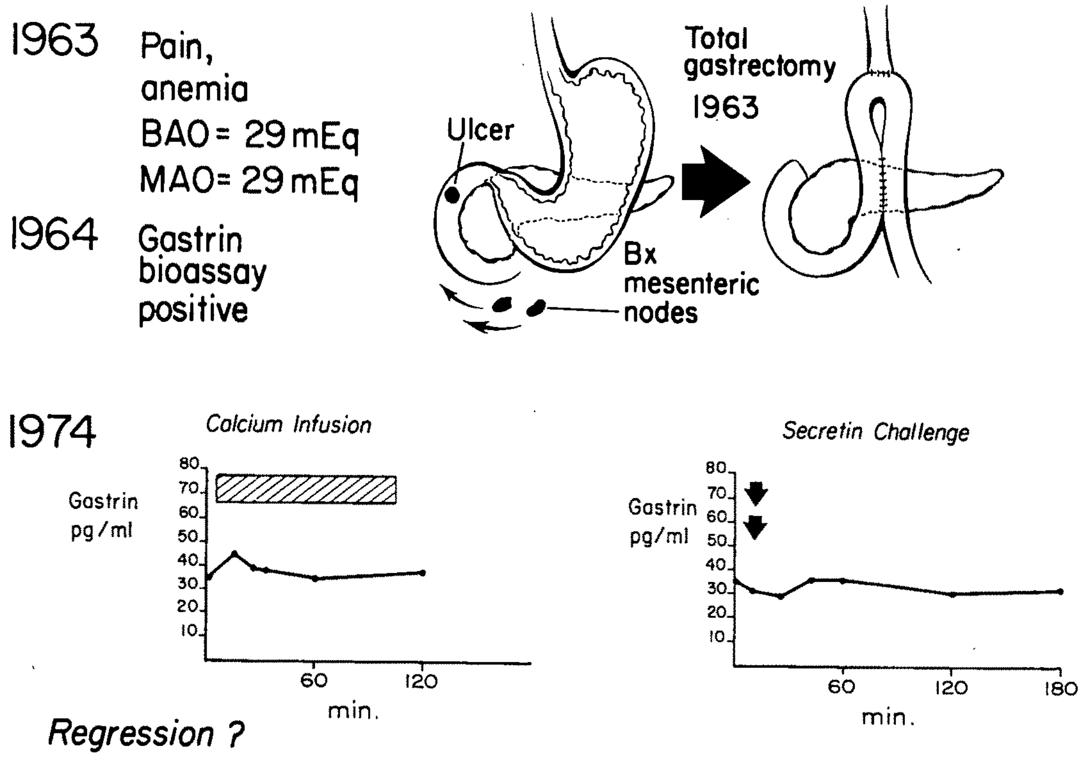

FIG. 6. Reg. No. 311. M. S., an 11-year-old boy who had a two-year history of anemia and epigastric pain.[21] Gastrointestinal radiographs showed a large duodenal ulcer, gastric hyperrugosity and hypermotility of small intestine—findings suggestive of Z-E syndrome. Gastric secretory studies supported the diagnosis. At operation in 1963, two excised mesenteric lymph nodes contained metastatic islet-cell carcinoma. The primary tumor was not found. Total gastrectomy was done. One year later, a bioassay for elevated serum gastrin was positive. The patient has remained well and free of recurrent tumor for 11 years. During the past five years, gastrin levels determined by radioimmunoassay methods have been low normal. Calcium infusion and secretin challenge tests in 1974 failed to show a rise in serum gastrin which would indicate residual tumor.

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DISCUSSION

DR. JAMES C. THOMPSON (Galveston): In our series of 13 ZE patients all but one has had a very high postoperative serum gastrin level. Therefore, leaving any parietal cells in the patient would invite recurrent ulcer. Time and again we have been shown the wisdom of the original admonition that we should do a total gastrectomy, and the present paper confirms that.

The only patient in whom we had a normal serum gastrin after operation was a patient in whom we found a small tumor in a paraduodenal node. Dr. Fox has assumed that these small ectopic tumors are due to occult metastases. I would like to make an alternative assumption that it is a primary tumor in an ectopic piece of pancreas. This assumption is supported by the finding of a normal level of serum gastrin the next day. Gastrin has remained normal to the present and I think that in patients with small ectopic tumors excision of the ectopic nodule may remove the only tumor present.

I have a question: Are duodenal tumors different? They are the only possible exception to the rule that we should do a total gastrectomy. Dr. Oberhelman has found that enucleation is effective. I'd like to know what information you have on that point.

We have treated patients with hepatic metastases with intrahepatic artery infusions of 5-fluorouracil, and I wonder if there is any information in the registry on that point.

I am skeptical of the "gastric factor." Perhaps the higher death rate from tumor in the group of patients who had less than a total gastrectomy was due to pre-selection; that is, perhaps when a surgeon found that his patient had a large nonresectable hepatic metastasis, perhaps he was disinclined to do a total gastrectomy, and this would bias the series. Indeed, the presence of a large hepatic metastasis may have been *the* indication for a lesser procedure in some or most cases.

I question the significance of the tumor regression in three patients. All have tumor now, so that the regression was only temporary; and if it's real, why does it occur in only three of 137 patients?

The behavior of hepatic metastases in Zollinger-Ellison syndrome is similar to that of carcinoid tumors. This is not surprising, since they have a common stem cell origin, and they are indistinguishable histologically. Carcinoid tumors have been found to be quiescent for years, and then to undergo growth spurts and to kill their host. No one has invoked a feedback inhibition of carcinoid tumor growth, and I'm not sure that we need to invoke what seems to me to be a fairly mystical concept of feedback inhibition of ZE tumors.

DR. STANLEY R. FRIESEN (Kansas City, Kansas): This paper confirms the beneficial effect of total gastrectomy in patients with Zollinger-Ellison syndrome. I'm sure that the total gastrectomy does produce regression and lack of progression in a few patients; other patients may have exceedingly slow growth as seen in the comparative curves in the paper. There may be abnormal feedback mechanisms which are involved in the pathogenesis of the Zollinger-Ellison syndrome or in the regression that one occasionally sees after total gastrectomy, such as an abnormal duodenal secretin feedback mechanism which is totally obliterated after total gastrectomy and after vigorous antiacid therapy.

But the inter-relationships between the endocrine glands in the foregut are also important, because progression of tumor which is occasionally seen also after total gastrectomy has been related to the development or association of other foregut tumors, including pituitary tumors.

Regression and lack of progress have been defined in the manuscript of this paper, and I think it's difficult to tell which one is occurring. One of our problems is the difficulty in differentiating between a metastasis and a mesodermal rest near the pancreas.

Either regression or lack of progression may occur for long periods of time, but if we follow the patients long enough, I think we will find that other endocrine tumors will occur, and these may appear to be recurrences.

In this series of four patients that Dr. Fox presented, two have seemed to have had recurrences, but the tumors have been a different foregut tumor when they came back. I'd like to show two slides of these two patients.

(Slide) This patient is one who begins with hyperparathyroidism, and after removal of four of his hyperplastic parathyroid glands, one of which was adenomatous, his hyperparathyroidism disappears. He had a total gastrectomy in 1967 for primaries in his pancreas, and metastatic tumors in his liver and lungs. Total gastrectomy caused visible diminution and, at a second look, disappearance of tumor in the liver and in the lung. He had a single recurrence later and an excision, with documentation of this gastrin-secreting tumor.

He progressed six years without evidence of recurrent tumor and with relatively normal serum gastrin levels. After six years the serum gastrin level goes up, his serotonin level goes up, and he is found to have duodenal carcinoid tumors which contain and secrete glucagon in excess.

His serum gastrin levels and his glucagon values now are normal after removal of the duodenal carcinoid tumors. He probably will develop another tumor as time goes on.

(Slide) This is one other patient included in the study by Dr. Fox. He begins with Cushing's syndrome, develops Zollinger-Ellison syndrome with high acids, and with lymph node, liver and pulmonary metastases. This liver metastasis is excised for biopsy, and a total gastrectomy is done in 1961. In five years he has a second-look procedure, with no liver metastases seen; but on the second-look procedure of his chest he has mediastinal nodes' which are excised. But later there is persistence of a mediastinal tumor, biopsied, but non-resectable, and a hypophysectomy is done in 1968.

The pituitary excision done at this time is followed by a decrease in the size of the biopsied mediastinal tumor. The serum gastrin levels come down to normal, but in 1973 the serum gastrin becomes suddenly elevated and he dies within a few months with recurrent mediastinal tumor in spite of chemotherapy and radiotherapy.

The interesting thing is that at autopsy there was no tumor in his abdomen except two very small tumors in his pancreas and no liver metastases. There was tumor in his upper chest and neck and these did not contain gastrin. There was parafollicular calcitonin cell hyperplasia, islet cell hyperplasia, and the two parathyroid glands that remained showed chief cell hyperplasia.

In other words, he has 12-year regression after total gastrectomy and a five-year regression after hypophysectomy, only to have a tumor recur which does not appear to be the same type of tumor. This suggests a genetic basis for hyperplasia and tumor growth in patients who have foregut abnormalities.

DR. STUART D. WILSON (Closing discussion): The problem in assessing whether there has been "regression" or even a "lack of progression" in the ZE patient who has only tumor found in lymph nodes is a very difficult one. Only recently, since we have had sensitive radioimmunoassays for gastrin, have we been able to precisely measure elevated gastrin levels in patients. I think now that with these assay methods available and with the new calcium and secretin challenge techniques, one of which Dr. Thompson has brought to us, we may be able to answer this question. If these patients are studied immediately following surgery and the gastrin levels are elevated, particularly after secretin or calcium challenge tests, and then over a period of time the gastrin falls to normal and challenge tests do not stimulate abnormal gastrin responses, then I think such findings would suggest regression. If lymph nodes only were removed at the time of surgery and gastrin was normal after surgery, then perhaps the tumor in the nodes represents "primary tumor".

Of course, this is one reason why Dr. Fox chose to look at the subgroup of patients who had documented metastasis to the liver. These patients were known to have residual tumor after total gastrectomy and evaluation of regression would be somewhat easier.

To answer the question about duodenal wall tumors, Dr. James Hofmann has looked at this group of patients in the Z-E Tumor Registry and 103 of 800 patients with proven Z-E syndrome had duodenal wall tumors. This is approximately 13%, so I think it is worthwhile for the surgeon operating on a patient suspected of harboring a gastrinoma to examine this area very carefully; in fact, even doing a duodenotomy and palpating inside the lumen if tumor cannot be found. In that group of 103 patients there were 48 patients who had single duodenal wall tumors; 24, or about a fourth, had associated pancreatic tumor, and another 25 per cent had associated lymph node tumor. So, local excision of a duodenal wall tumor would not have been successful in about one-half of the cases. Indeed, in more than one-half of the ZE patients recorded in which local excision without total gastrectomy was attempted, there was failure. There have been only 20 patients in which local excision of duodenal wall tumors has been successful and some of these patients have only short-term followup.

We do not have good data on the usefulness or the choice of chemotherapeutic drugs to use in patients with liver metastasis.

Dr. Friesen brings up a very good point about associated endocrine tumors. He has very nicely documented in several of his publications that ZE patients often harbor other endocrine abnormalities and they should be evaluated both during their initial workup and during followup for other hormone excesses. In 1964 when we presented the first ZE Registry report before this Association, the incidence of endocrine abnormalities was reported as 20%. This has now risen to 30%. I think this increase is due, in part, to better reporting but also because other endocrine abnormalities have surfaced in these patients as they have been followed over the years.

Effect of Preoperative Antibiotic Regimen on Development o Infection after Intestinal Surgery:

Prospective, Randomized, Double-Blind Study

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A prospective, randomized, double-blind study was performed to compare preoperative antibiotic preparation with neomycin (group 1), neomycin and tetracycline (group 2), and placebo (group 3) in patients undergoing elective intestinal surgery. The 196 patients were approximately equally distributed among the three study groups, which proved similar to each other in terms of age, sex, diagnosis, site of lesion, and operative procedure. There were significantly ($P < 0.01$) fewer patients with postoperative wound sepsis in the neomycin-tetracycline group (group 2) than in either of the two other groups. Postoperative wound infection rates in groups 1 and 3 were nearly identical. Most infections contained both aerobic and anaerobic bacteria. Eight of nine episodes of septicemia due to *Bacteroides fragilis* occurred in patients in groups 1 and 3.

THE ROLE of intestinal antisepsis in preventing postoperative septic complications remains controversial. Yale and Peet[25] emphasized the need for carefully designed, rigidly controlled, prospective, randomized, double-blind, clinical studies of the effects of antibiotics on postoperative wound sepsis. As pointed out by Nichols and Condon[18] in a review of preoperative preparation of the colon, nearly all clinical studies on this subject have been retrospective and poorly controlled.

Between 1968 and 1971, a prospective, randomized, double-blind investigation of patients admitted for elective colonic and rectal surgery was carried out at the Mayo Clinic. This paper presents the results of this investigation on 196 patients.

Methods and Materials

Between 1968 and 1971, patients scheduled for elective intestinal surgery by one of the investigators (E.S.J.) were assigned, on a randomized and double-blind basis to three preoperative medication groups: neomycin (group 1), neomycin plus tetracycline (group 2), and placebo (group 3). At the time of the patient's admission to the hospital, the hospital pharmacist was notified, and he placed the patient into one of the medication groups on the basis of a prearranged randomized scheme.

The standard preoperative preparation consisted of the following: a residue-free diet for 48 hours; buffered aqueous solution of sodium phosphate and biphosphate (Phospho-Soda), 16 ml twice daily for 48 hours; two tap-water enemas 2 days preoperatively and two tap-water enemas in both the morning and the afternoon 1 day preoperatively; and the randomly assigned oral medication given as three capsules four times daily for 48 hours. These medications were packaged in such a manner that each patient received one envelope containing 24 identical capsules, divided into packets of three capsules each, to be taken during the 48 hours prior to operation. The contents of the capsules received by each patient remained unknown to the patient, his physicians, and the investigators until the study was completed.

Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

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TABLE 1. *Age and Sex Distributions of Patients, by Medication Group*

Age (decade)	Patients (no.) Neomycin Group 1	Neomycin-tetracycline Group 2	Placebo Group 3
20–29	5	1	2
30–39	3	4	4
40–49	8	9	3
50–59	14	16	18
60–69	23	24	23
70–79	14	10	11
80–89	1	1	2
Total	43 M; 25 F 68	33 M; 32 F 65	34 M; 29 F 63

Patients in the placebo group (group 3) received capsules containing 250 mg of lactose. In the neomycin group (group 1), the three capsules in each packet consisted of two containing 250 mg of neomycin and one containing 250 mg of lactose. In the neomycin-tetracycline group (group 2), two of the capsules contained 250 mg of neomycin and one contained 250 mg of tetracycline.

All operations were performed by one surgeon (E.S.J.). Pertinent preoperative, operative, and postoperative clinical and laboratory data were entered on data sheets for analysis by a computer program.

Isolation and identification of bacteria were performed by standard methods as described in the *Manual of Clinical Microbiology*.[1] An anaerobic jar (GasPak, BBL) technique was used for recovery of anaerobes,[14] and methods for identification of anaerobes were those described by Dowell and Hawkins.[5]

Results

Patients who had received antimicrobial agents, other than those included in the protocol, preoperatively or during operation were eliminated from the study, as were those who, for one reason or another, did not complete the entire preoperative preparation protocol. This left 196 patients who were eligible for the study: 68 in the neomycin group, 65 in the neomycin-tetracycline group, and 63 in the placebo group. The age and sex distributions of the patients (Table 1) were similar in each medication group, with the exception of a predominance of males in the neomycin group. Most of the patients were in their sixth, seventh, or eighth decade (group 1, 75%; group 2, 77%; and group 3, 83%).

TABLE 2. *Diagnoses in Each Medication Group*

Diagnosis	Patients (no.) Neomycin Group 1	Neomycin-tetracycline Group 2	Placebo Group 3
Carcinoma	33	27	31
Chronic ulcerative colitis	6	3	2
Diverticulitis	6	11	13
Polyp	14	10	10
Rectal prolapse	0	1	1
Cyst	1	0	0
Regional enteritis	4	1	3
Lipoma	0	1	0
Multiple colonic polyps	0	0	1
Leiomyosarcoma, ileum	0	1	0
Postradiation stricture	0	1	0
Ileocolitis	0	2	1
Other	4	7	1
Total	68	65	63

The diagnoses are listed in Table 2. The most frequent diagnosis in each group was carcinoma, followed by colonic polyps and diverticulitis. The sites of the lesions for which patients in each group were operated on are listed in Table 3. The most commonly involved site was the rectosigmoid. The types of operations performed on patients in each group are listed in Table 4 and were similar in distribution in each group.

In Table 5 are listed the results of bacteriologic studies of feces removed from the intestinal lumen at operation. There were only four patients in group 2 with cultures yielding anaerobic bacteria. Cultures from two of these yielded *Bacteroides fragilis* only in anaerobic cultures; cultures from two other patients yielded, in addition to *B. fragilis*, *Peptostreptococcus*, and, in one case, *Eubacterium tortuosum*. There were 10 patients each in groups 1 and 3 from whom operative fecal samples contained *B. fragilis*. Other anaerobic bacteria, isolated from a few patients only, included *B. oralis*, *Bacteroides* spp., *Fuso-*

TABLE 3. *Sites of Lesions in Each Medication Group*

Site	Patients (no.) Neomycin Group 1	Neomycin-tetracycline Group 2	Placebo Group 3
Small intestine			
Ileum	4	2	3
Large intestine			
Appendix	1	0	0
Ascending colon	8	5	7
Transverse colon	3	6	3
Descending colon	4	4	5
Sigmoid colon	5	5	7
Rectosigmoid	27	21	23
Rectum	8	10	7
Combined			
Entire colon	4	1	2
Ileum & colon	1	4	1
Ileum & colon & rectum	0	0	0
Colon & rectum	1	1	1
Other	2	3	2
No lesion	1	1	0
Carcinomatosis	1	0	0
Adhesions	0	1	1
Gallbladder	0	1	0
Endometrium	0	0	1
Total	68	65	63

bacterium nucleatum, F. necrophorum, Clostridium perfringens, C. difficile, anaerobic cocci, and nonsporulating gram-positive bacilli.

The aerobes most commonly recovered from this material were group D streptococci (7 patients in group 1, 7 in group 2, and 10 in group 3) and *Escherichia coli* (8 patients in group 1, 10 in group 2, and 17 in group 3). *Klebsiella pneumoniae* was recovered from six patients in group 3, in contrast to none in group 1 and one in group 2. *Staphylococcus aureus* was not isolated from any of these samples. *Candida albicans* was isolated from 2 patients in group 1, 12 patients in group 2, and none in group 3.

The postoperative complications encountered in each group are listed in Table 6. The most significant difference among the groups was in the number of patients with wound infections: 28 and 27 patients in groups 1 and 3, respectively, in contrast to only 3 patients in group 2. The bacteria isolated from the postoperative wound infections are listed in Table 7. Anaerobic cultures of the infected wounds of all three patients in group 2 contained *B. fragilis;* it was present with *Eubacterium limosum* in one patient, with *B. melaninogenicus* and *F. necrophorum* in one, and with *C. perfringens* and *Peptostreptococcus* in one. Among the aerobes, *E. coli* was isolated from wound infections of 10, 3, and 16 patients in groups 1, 2, and 3, respectively.

There were 10 patients with postoperative septicemia: 4 patients in group 1 with *B. fragilis,* 1 patient each in group 2 with *B. fragilis* and *K. pneumoniae,* and 4 patients in group 3 with *B. fragilis.* Seven of the nine patients with *B. fragilis* septicemia also had *B. fragilis* in postoperative wound infections.

Among the 196 patients in the study, 9 died: 2 in group 1, 2 in group 2, and 5 in group 3. Of the two deaths in group 1, one was due to a pulmonary embolus 27 days postoperatively and one was due to peritonitis secondary to intra-abdominal abscess (autopsy permission denied). The two deaths in group 2 were related to myocardial infarction and to femoral arterial thrombosis, respectively. There were two patients in group 3 who at autopsy had peritonitis and one who had a retroperitoneal abscess. One patient in group 3 died of *Candida* septicemia and had multiple organ abscesses at autopsy. There was one death in group 3 due to myocardial infarction immediately after operation.

Discussion

In recent years, studies of fecal flora by means of anaerobic techniques and selective media have shown that anaerobic bacteria constitute the predominant microflora in normal human feces.[6,8,9,16] Numerous clinical studies have been reported in which a variety of antimicrobial agents have been used for intestinal antisepsis. These have been reviewed by Nichols and Condon[1 and by Yale and Peet.[25] Most of these studies have beer retrospective and have been poorly controlled. In one recently published, prospective, randomized study of 2(patients admitted for elective colon resection, Nichol: *et al.*[17] found that, in 10 patients receiving three doses o neomycin and erythromycin 1 day preoperatively, there was suppression of colonic aerobes and anaerobes anc there were no wound complications. Although the difference between total colonic microflora in this grouj and in the group receiving no preoperative antibiotic: was highly significant, the difference in rates of wounc sepsis between the two groups was not significant.

In the present study, a prospective, randomized double-blind investigation of 196 patients undergoin elective colonic and rectal surgery was successfully completed. These patients were divided more or les: equally into three study groups. Their ages and sexe: were similarly distributed among the three groups, except for a predominance of males in group 1 (neomycir alone). The diagnoses in each group were similar ir distribution, as were the sites of the lesions and th

TABLE 4. *Types of Operations Performed in Each Medication Grou*

Procedure	Patients (no.) Neomycin Group 1	Neomycin-tetracycline Group 2	Placebo Group 3
Combined abdomino-perineal	8	4	5
Resection	33	33	35
Colectomy	0	0	0
Coloproctectomy & ileostomy	4	3	2
Colotomy	14	10	10
Closure, colonic stoma	3	6	3
Bypass, palliative	2	1	2
Exploration	4	6	5
Colostomy	0	1	0
Ventral suspension fixation	0	1	1
Total	68	65	63

TABLE 5. *Bacteriologic Studies of Feces Obtained From Intestina Lumen at Operation*

	Neomycin Group 1	Neomycin-tetracycline Group 2	Placebo Group 3
Patients with cultures (no.)	26	25	32
Total cultures (no.)	26	25	32
Positive cultures (no.)	15	12	19
Patients with positive cultures (no.)	15	12	19
Patients with cultures yielding anaerobes (no.)*	10	4	15
Patients with cultures yielding aerobes (no.)†	11	9	18

* Difference between groups 2 and 3 is significant ($P < 0.01$

† Difference between groups 2 and 3 is of borderline significanc ($P < 0.05$).

TABLE 6. *Postoperative Complications in Each Medication Group*

Complication	Patients (no.) Neomycin Group 1	Neomycin-tetracycline Group 2	Placebo Group 3
Wound infection*	28	3	27
Peritonitis	1	0	5
Wound separation	4	0	0
Septicemia	4	2	4
Fecal fistula	1	0	7
Urinary tract infection	8	6	12
Ileus	0	0	1
Staphylococcal enteritis	0	0	0
Pseudomembranous enterocolitis	0	0	0
Cardiac problem	2	2	3
Stroke	0	0	0
Pneumonia	1	0	3
Pulmonary embolus	0	0	0
Renal failure	0	0	0
Hepatic failure	0	0	0

* Difference between group 2 and groups 1 and 3 is significant ($P < 0.01$).

types of operations performed. All of the operations were performed by one surgeon in order to minimize variation of the protocol. The role of preoperative oral antimicrobial preparation in tumor implantation in the anastomotic line[2,10,23] was not investigated.

Because reports from this institution[4] and elsewhere[3,8,12] had shown that neomycin and tetracycline suppress both aerobic and anaerobic fecal microflora, it was decided to examine these drugs in combination and to compare patients so prepared (group 2) with those prepared with neomycin alone (group 1) and with those receiving no antibiotic preparation at all (group 3).

Anaerobic jar techniques and selective media were introduced into this laboratory on a routine basis in 1968, prior to the beginning of this study. Although it is recognized that anaerobic chamber techniques represent a more optimal approach to the study of intestinal flora,[21] it has been shown by Rosenblatt *et al.*[20] and by Killgore *et al.*[11] that anaerobic jars are just as effective as the more complex roll-tube and chamber methods for recovering clinically significant anaerobes. Therefore, it is assumed that the recovery of anaerobes from clinical specimens was satisfactory but that their recovery from the intestinal content sampled at operation probably was not.

Operative fecal cultures were not done for all patients; however, among the 83 for whom they were done, there was a statistically significant decrease in cultures yielding anaerobes in group 2 compared with group 3. The most striking difference among the study groups, however, was the significantly fewer patients with postoperative wound infections in group 2. The numbers of patients with postoperative wound infections in groups 1 and 3 were nearly identical. Although all but two of the infected wounds contained mixed flora, it is interesting that not only were there significantly fewer wound infections in group 2 but also that there were few anaerobes involved. The role of tetracycline in decreasing the number of infections and the number of anaerobes isolated from these infections is not unlike that exerted by clindamycin in a study of infections occurring after penetrating abdominal trauma.[22] Just why suppression of anaerobes should so significantly affect the frequency of wound infections remains unknown. Synergic mechanisms in certain mixed infections

TABLE 7. *Bacteria Isolated From Postoperative Wound Infections*

Neomycin Group 1 Organism	Pt. (no.)	Neomycin-tetracycline Group 2 Organism	Pt. (no.)	Placebo Group 3 Organism	Pt. (no.)
		Aerobes			
Escherichia coli	10	*E. coli*	3	*E. coli*	16
Enterobacter	1	*P. mirabilis*	1	*Enterobacter*	2
Proteus mirabilis	1	*S. epidermidis*	1	*P. mirabilis*	2
Staphylococcus epidermidis	7	*Pseudomonas aeruginosa*	1	*Staphylococcus aureus*	1
Streptococcus, β hemolytic	1	Streptococcus, group D	1	*S. epidermidis*	10
Streptococcus, group D	7	Streptococcus, viridans group	1	*P. aeruginosa*	2
Streptococcus, viridans group	5			Streptococcus, group D	4
Corynebacterium	2			Streptococcus, viridans group	7
Klebsiella pneumoniae	3			*K. pneumoniae*	6
Proteus morganii	1			*Corynebacterium*	1
		Anaerobes			
Bacteroides fragilis	16	*B. fragilis*	3	*B. fragilis*	18
Clostridium perfringens	4	*C. perfringens*	1	*C. perfringens*	4
Bacteroides melaninogenicus	2	*B. melaninogenicus*	1	*B. melaninogenicus*	2
Fusobacterium nucleatum	1	*F. necrophorum*	1	*P. acnes*	1
Propionibacterium acnes	1	*Peptostreptococcus*	1	*Bacteroides succinogenes*	2
Peptostreptococcus	1	*Eubacterium limosum*	1	*Clostridium* sp.	1
Peptococcus	2			*Peptostreptococcus*	6
Fusobacterium necrophorum	2			*Peptococcus*	1
Clostridium difficile				*F. necrophorum*	1
Bacteroides spp.	2				

were reviewed by Roberts[19] who concluded that, in general, the organisms responsible for mixed infections are individually either nonpathogens or weak pathogens and that a deficiency in infectivity or virulence of each individual organism must be compensated for by at least one other member of the group that is competent in that respect.

The fact that 9 of the 10 cases of septicemia were due to *B. fragilis* is notable but not surprising in view of the well-known association between this condition and underlying gastrointestinal disease, particularly malignancy and surgery.[7,13,24] In reviewing anaerobic infections in the compromised host, Finegold *et al.*[7] suggested that the preoperative use of antimicrobial agents may be an important predisposing factor to anaerobic infections; however, this association was primarily due to the use of aminoglycosides alone, to which *B. fragilis* and most other anaerobes are resistant.[15]

This investigation clearly showed significantly fewer postoperative wound infections in the group of patients receiving neomycin and tetracycline than in the groups of patients receiving neomycin alone or placebo. This decrease occurred despite the fact that only a third of the clinical isolates of *B. fragilis* tested during 1971 in this laboratory were susceptible to tetracycline.[15] Whether or not the parenteral administration of kanamycin and clindamycin would be more beneficial in decreasing postoperative wound infections after elective colonic surgery, as it appears to have been after penetrating abdominal trauma,[22] is not currently known but probably bears investigation. Nonetheless, the inescapable conclusion of this study is that preoperative antibiotic preparation with neomycin and tetracycline is indicated when elective intestinal surgery is planned in the types of patients represented in this study and that this preparation does not predispose to other serious infection due to staphylococci or yeasts.

Acknowledgment

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DISCUSSION

DR. ISIDORE COHN, JR. (New Orleans): This is a slide we put together some time ago, showing the various studies from single institutions where there were comparative studies of patients with and without preoperative bowel preparation; and except for one single institution, you see that each institution reported a lower incidence of wound infection, peritonitis, and so forth, on patients who were prepared, as compared with the patients who were not prepared.

However, the trouble with every study on this slide is that each and every one is a retrospective study, and therefore, according to the statisticians, really not comparable sets of data.

We have been going on for far too many years worrying whether we should use intestinal antiseptics. The experimental data is very clear, and up to this time the clinical data has been pointing in the direction that Dr. Judd has reported today.

The study he has reported is beautiful for the following reasons. It is a prospective, randomized study, which is what all of us have been asking for and none of us have been doing. It has been conducted in a single institution, to minimize some of the problems that occur in interinstitutional studies. It has been completed in a short enough time span that probably there have not been significant changes in technique during the time the study was conducted. And, finally, one point that probably is not likely to be repeated anywhere else: All of the surgery was conducted by a *single surgeon.*

So we have got a study that answers just about all of the criteria one could ask for, and the result of this study is an indication that preoperative intestinal antisepsis *is* of value by statistical evaluation. That is a very important fact.

Insofar as I can tell, there is only one other prospective, randomized study comparable to this. It was reported in the *British Journal of Surgery* in 1971. The results are entirely comparable to those reported today by Dr. Judd.

I have one minor criticism. I would not pick the combination of antibiotics that he has used—neomycin and tetracycline—as the ideal agents for intestinal antisepsis. It is true we used them on our own service for several years. We no longer think they are the ideal combination. In the face of a study like this, that's a very minor criticism. The important point that Dr. Judd has made is that on the basis of a well-designed scientific study intestinal antiseptics are valuable.

DR. ALLEN M. BOYDEN (Portland, Oregon): If a survey of the membership who do colon surgery were taken there would be little unanimity regarding preoperative bowel preparation. The problems of overgrowth of pathogenic bacteria have resulted from prolonged use of antibiotics. We all know Dr. Altemeier's work.

For many years I used simple cleansing with catharsis and enemas without the addition of antibiotics. However, after the report by Dr. Nyhus and his associates last year at this meeting of the use of neomycin and erythromycin given only during the 18 hours preceding operation with the essential elimination of pathogens from the bowel, and remarkable reduction in wound infections, I have followed this routine. I am happy to report that since adopting this method I have had no wound infection after colon resection.

Dr. Judd's report is most interesting since he also attained a marked reduction in wound infections. Furthermore, his cultures revealed a significant reduction of anaerobic bacteria in bowel prepared with neomycin and tetracycline, yet tetracycline is not specific for most anaerobic organisms. I would ask him if he can tell us why this should be true.

Cleansing the bowel is, of course, most important. I have avoided the use of castor oil because of its profound irritative effect on the gut. Some years ago I had occasion to operate on a patient within a few hours after a large dose of castor oil. The severe reaction with grossly visible hyperemia and edema convinced me that less drastic measures might be less disturbing. Mild catharsis and cleansing enemas along with a clear liquid diet have sufficed to produce a clean empty bowel.

DR. LLOYD M. NYHUS (Chicago): Following the leadership of Dr. Ronald Nichols, we have supported the use of oral, nonabsorbable antibiotics for preoperative colon preparation. We have stressed that the antibiotics chosen should provide uniform suppression both of the colonic aerobes and the predominant colonic anaerobes, such as *Bacteroides fragilis.*

Previous studies reported on antibiotics susceptibility by Kislak and Martin, Gardner and Washington, show that tetracycline, given at therapeutic levels, inhibited only about 40% of the *Bacteroides fragilis* organisms, while erythromycin at the same concentration inhibited 92% of the organisms. Other authors have noted a high percentage of resistance of Bacteroides fragilis organisms to tetracycline.

Thus we have chosen to employ erythromycin base in our bowel preparation, because it is highly effective against colonic anaerobes.

(Slide) Remember our 69 patients without wound infection presented to this meeting last year?

(Slide) You will note that subsequently we have used the same preparation in 104 patients. We now have two wound infections, one *E. coli* and one staphylococcus, and no septicemia.

The authors are to be congratulated for their well-controlled study. Could they please indicate why they did not use erythromycin in conjunction with neomycin for their Group II patients, since their *in vitro* studies clearly showed the superiority of erythromycin over tetracycline against the anaerobes *Bacteroides fragilis.*

DR. EDWARD S. JUDD [Closing discussion]: Dr. Boyden asked a question about the anaerobes. I might answer that with a note that Dr. Bill Altemeier left for me before returning to Cincinnati.

> As you know, I have used tetracycline intravenously just before, during and for 4 days postoperatively for its effect on the bacteroides and the clostridia. You have used the intestinal route, and the results are just as critical to me, and for the same reasons.

Dr. Nyhus asked about erythromycin. We were going through the throes of getting a grant and getting everything started, and we were so delighted to get what we got that we settled for what we had.

The Metabolic Basis of Portasystemic Encephalopathy and the Effect of Selective vs Nonselective Shunts

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JOHN T. GALAMBOS, M.D., ATEF A. SALAM, M.D., ROBERT B. SMITH, III, M.D.

Portasystemic encephalopathy has been a major deterent to the utilization of total or non-selective shunts. A procedure to determine the maximum rate of urea synthesis (MRUS) has been developed and a depression in the ability to synthesize urea has been shown to correlate closely with the development of encephalopathy. Utilizing this procedure and a modified ammonium tolerance curve, a controlled comparison was instituted between selective and non-selective shunts. Following a non-selective or total shunt, there was a definite deterioration in both the MRUS and the ammonium chloride tolerance curve which was accompanied by a high rate of clinical encephalopathy. In marked contrast, the selective shunt, which maintains portal venous perfusion of the liver, showed little or no change in the MRUS and the ammonium chloride tolerance curve following the selective shunt and there was a very low incidence of encephalopathy. The difference between the non-selective and selective shunt in maintenance of urea synthesis, metabolism of ammonium chloride, and the development of clinical encephalopathy show the selective shunt procedure to be definitively superior in this regard.

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ENCEPHALOPATHY is a well-known complication of portasystemic shunt procedures.[2,4,13] Although recognized in 1892 by Pavlov in dogs with portacaval shunt,[6] postoperative encephalopathy was not clinically appreciated until the resurgence of shunt procedures for the treatment of gastroesophageal varices in the 1940's.[1,19,20]

Although Pavlov described postoperative changes in his experimental animals as "meat intoxication," the concept that hepatic encephalopathy is a syndrome of altered nitrogen metabolism has only recently been accepted. Rudman[11] has quantitatively documented the decreased capacity of patients with cirrhosis to catabolize protein to urea (Fig. 1). The maximal rate of urea synthesis after protein loading provides a sensitive and quantitative test to study the pathophysiology of cirrhosis and encephalopathy.[10]

Conventional operative procedures for decompression of gastroesophageal varices, such as portacaval or mesocaval shunts, are total or *nonselective* shunts in that portal perfusion of the liver is not preserved. Although highly effective in control of gastroesophageal bleeding, such shunts have been followed by a high incidence of encephalopathy.[13] In 1966, a new operative procedure was devised which was designed to decompress gastroesophageal varices but maintain portal perfusion of the liver. This operation, commonly referred to as selective distal splenorenal shunt, has been shown to be very effective in the control and prevention of hemorrhage from gastroesophageal varices.[17] The purpose of this report is to compare the effects on nitrogen metabolism of selective and nonselective shunts as determined by study of maximal rate of urea synthesis, ammonium chloride tolerance, and the clinical development of portasystemic encephalopathy.

Methods

Patient Populations

Two patient populations had metabolic studies. Population A represents 18 patients evaluated both before

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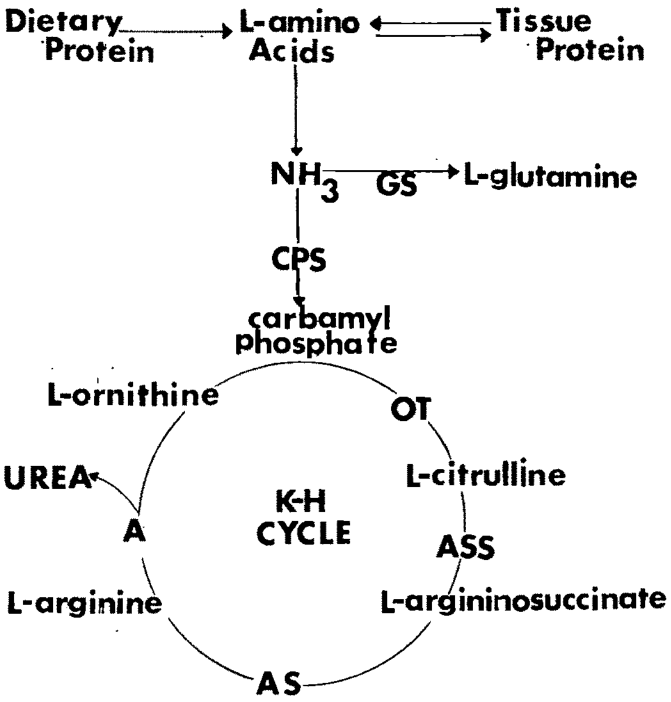

FIG. 1. Protein Catabolism: the Krebs-Henseleit (K-H) cycle. Enzymes are glutamine synthetase (GS); carbamyl phosphate synthetase (CPS); ornithine transcarbamylase (OT); arginiosuccinic acid synthetase (ASS); argininosuccinic acid lyase (AS); arginase (A).

and after surgery. Patients were randomized at surgery by closed envelope method prepared by the Department of Biometry for selective (n = 9) or nonselective shunt (n = 9). Population B comprises 19 additional patients who were not randomized and were studied postoperatively (in addition to the 18 in population A) but not preoperatively. Although not clinically encephalopathic prior to surgery, population B patients could have been undetected preclinical encephalopathics. Preoperative and postoperative evaluations were done zero to one month before, and three to seven months after surgery, respectively. All patients had normal renal function and no ascites when studied. In addition, all patients (n = 34) in the randomized study were evaluated clinically (Table 5).

Both populations of patients studied metabolically were evaluated in four ways during a 14-day admission to the metabolic research unit: 1) Child's clinical classification was determined; 2) Presence of encephalopathy by the clinical and electroencephalographic criteria of Parsons *et al.*;[7] 3) The maximal rate of urea synthesis (MRUS, normal values = 55–70 mg urea N/h/kg $BW^{3/4}$); and 4) NH_4Cl sensitivity (normal values > .21g NH_4Cl/kg $BW^{3/4}$). All tests were determined after equilibration on a 40 g protein diet. Patients received 6 g of neomycin by mouth daily.

MRUS Protocol. Maximal rate of urea synthesis (MRUS) was determined after ingestion of casein hydrolysate (0.94g protein N/kg $BW^{3/4}$) or intravenous administration of a solution of crystalline amino acids (FreAmine, 110 mg amino acid N/h/kg $BW^{3/4}$). Urea synthesized, but not excreted, was determined by measuring increase in plasma urea nitrogen distributed in total body water.[8] Urea hydrolyzed by intestinal bacterial urease was measured by recovery in the urine of a tracer dose of ^{14}C-urea given intramuscularly at the start of the test period. MRUS is calculated from the following formula:

$$\text{MRUS} = ([\text{mg urea N excreted between 8 and 24 h}] + [\text{BUN}_{24\text{h}}-\text{BUN}_{8\text{h}}]\ [\text{body water}]) \times (100/\%\ \text{recovery}\ ^{14}\text{C-urea}) \times (1/\text{kg BW}^{3/4}) \times (1/16\text{h}) = \text{mg urea N/h/kg BW}^{3/4}$$

Ammonium Chloride Tolerance. Ammonium chloride tolerance was determined by measuring venous plasma ammonia fasting and two hours after ingestion of a standard dose of ammonium chloride (0.0025, 0.0050, 0.010, 0.021, 0.042, 0.084, 0.13, 0.17, 0.21 g/kg $BW^{3/4}$). The smallest dose of ammonium chloride producing a rise in plasma ammonia of 40 μg/100 ml defined ammonium chloride tolerance.

Results

Results are presented in four sections: 1) Pre- and postoperative Child's classification data in Population A (Table 1); 2) Pre- and postoperative MRUS data in Population A (Tables 2 & 3 and Fig. 2); 3) Pre- and postoperative ammonium chloride sensitivity in Population A (Tables 2 & 3); and 4) Incidence of postoperative encephalopathy, Population A plus Population B (Tables 1–4 and Fig. 3).

1. *Effect of Operation on Child's Classification (Table 1, Population A)*

Three patients with nonselective shunts had lower Child's classification after surgery than before operation. Three patients had no change; one patient improved. One patient with selective shunt had lower Child's classification after surgery than before operation. Five patients had no change; two patients improved.

2. *Effect of Operation on MRUS (Population A, Tables 2 &3) (Fig. 2)*

Maximal rate of urea synthesis before surgery was not significantly different in patients operated with nonselective shunt (n = 9, mean ± S.E., 40 ± 4.21) than in patients operated with selective shunt (46.5 ± 4.08, p = 0.25). Selective shunt did not significantly alter MRUS (n = 9, pre-op vs post-op MRUS, mean ± S.E.,

TABLE 1. *Non-metabolic Data Before and After Surgery (Population A)*

Before Surgery

Patient	Type of Surgery	Prothombin Time (100%)	Albumin (3.5–4.0)	SGOT (40)	Total Bilirubin (0.2–1)	Alkaline Phosphatase (30–85)	Child Group	Liver Biopsy
1.	NS	12.8/11.6	4.8	35	1.65	79	B	Cirrhosis
2.	NS	13.6/11	2.6	305	3.8	10.2 (KA)	C	Cirrhosis
3.	NS	12.9/11	3.8	47	3.8	21	C	Cirrhosis
4.	NS	14.2/11.6	3.2	44	2.1	95	B	Cirrhosis
5.	NS	13.4/11.6	3.4	75	1.5	90	B	Cirrhosis
6.	NS	12/11.3	4.6	38	1.2	67	A	Cirrhosis
7.	NS	14/11.5	4.0	33	1.4	65	A	Cirrhosis
8.	NS	12.6/11.6	3.0	55	0.5	15 (KA)	B	Cirrhosis
9.	NS	11.9/11.2	3.9	17	0.8	122	A	Cirrhosis
10.	S	12.9/11.2	4.6	51	2.25	290	B	Cirrhosis
11.	S	29.2/11.2	2.7	186	1.6	264	B	Cirrhosis
12.	S	12.3/11.6	3.4	47	1.25	164	B	Cirrhosis
13.	S	—	2.4	50	1.2	24	B	Cirrhosis
14.	S	12.9/11.6	3.3	167	4.4	330	B	Cirrhosis
15.	S	14.5/11.0	4.0	35	0.8	94	A	Cirrhosis
16.	S	13.5/11.6	3.6	45	1.2	112	A	Cirrhosis
17.	S	17.2/11.6	3.7	67	0.6	18.9 (KA)	A	Cirrhosis
18.	S	—	3.8	26	0.4	139	A	Cirrhosis

After Surgery

Patient	Prothombin Time	Albumin	SGOT	Total Bilirubin	Alkaline Phosphatase	Child Group	Change in Child Group	Encephalopathy
1.	—	2.2	21	2.1	115	C	—	+
2.	—	2.6	140	1.4	122	B	+	
3.	—	3.9	45	3.8	207	C	0	+
4.	—	—	—	—	—	—	—	
5.	15.9/11	3.2	236	4.7	120	C	–	+
6.	—	3.8	48	1.3	130	A	0	+
7.	15.6/11.3	3.3	69	1.45	83	B	—	
8.	13.2/11.2	2.3	45	0.3	124	B	0	+
9.	—	—	—	—	—	—	—	
10.	12.8/11.7	4.4	55	1.55	323	A	+	
11.	—	3.6	285	2.0	304	B	0	
12.	11.5/11.7	3.2	137	2.1	1038	B	0	
13.	—	—	196	—	—	—	—	
14.	13.0/11.7	3.8	73	–.95	105	A	+	+
15.	13.5/11.4	3.7	40	1.6	158	A	0	
16.	—	4.2	70	1.4	175	A	0	
17.	13.8/11.4	4.2	25	1.1	200	A	0	
18.	12.5/11.5	4.3	44	1.3	125	B	—	

TABLE 2. *MRUS and Ammonium Chloride Tolerance Before and After Surgery (Population A)*

	Before Surgery		After Surgery				
					% Change		
Patient	MRUS	NH_4Cl Tolerance	MRUS	NH_4Cl Tolerance	MRUS	NH_4Cl	Encephalopathy
1.	28	.084	14	.042	36	50	+
2.	60	—	60	—	0	0	
3.	60	—	20	—	67	—	+
4.	33	.13	30	.042	9	60	
5.	46	—	16	—	65	—	+
6.	46	—	23	—	53	—	+
7.	30	.17	27	.084	11	50	
8.	30	.17	17	.084	43	50	+
9.	27	.084	15	—	45	—	
10.	22	.042	22	.042	0	0	
11.	50	.21	44	.21	12	0	
12.	60	.21	58	.21	3	0	
13.	31	—	35	—	+13	—	
14.	51	—	49	—	4	—	+
15.	39	.13	33	.084	15	33	
16.	54	.17	34	.084	37	50	
17.	55	.17	55	.17	0	0	
18.	57	.21	57	.21	0	0	

TABLE 3. *Selective vs Nonselective Shunt, Change in MRUS, Ammonium Chloride Tolerance and Encephalopathy Significance*

	Preoperative (Mean ± S.E.)			Postoperative (Mean ± S.E.)		
	MRUS (mg Urea N/h/kg BW$^{3/4}$)	NH_4Cl Tolerance (g/kg BW$^{3/4}$)	Encephalopathy (Present/Absent)	MRUS	NH_4Cl Tolerance	Encephalopathy incidence/(%)
Selective	46.6 ± 4.08	0.16 ± 0.02	Absent	43.0 ± 3.99	0.14 ± 0.03	1 in 9 (11)
Nonselective	40.0 ± 4.21	0.14 ± 0.02	Absent	24.6 ± 4.51	0.06 ± 0.01	5 in 9 (55)

Change

MRUS			NH_4Cl Tolerance			Encephalopathy
Post-op—Pre-op Mean	(% Change)	(P)	Post-op—Pre-op Mean	(% Change)	(P)	
−3.5	(8%)	(0.50)	−0.02	(13%)	(0.6)	p = 0.01
−15	(38%)	(0.025)	−0.08	(42%)	(0.01)	

46.5 ± 4.08 vs 43.0 ± 3.99, p = 0.5). Contrastingly, nonselective shunt caused a significant decrease in MRUS (n = 9, pre-op vs post-op, mean ± S.E., 40 ± 4.21 vs 24.7 ± 4.51, p = 0.025).

3. *Effect of Operation on NH_4Cl Sensitivity in Population A (Tables 2 & 3)*

Ammonium chloride tolerance was not significantly different before surgery in patients operated with nonselective shunts (n = 4, mean ± S.E., 0.14 ± 0.02) than in patients operated with selective shunts (n = 7, mean ± S.E., 0.16 ± 0.02, p = 0.6). Selective shunt did not cause significant change in ammonium chloride tolerance (n = 7, pre-op vs post-op, mean ± S.E., 0.16 ± 0.02 vs 0.14 ± 0.03, p = 0.6). Nonselective shunt caused a significant decrease in ammonium chloride tolerance (n = 4, pre-op vs post-op, mean ± S.E., 0.14 ± 0.02 vs 0.06 ± 0.01, p = 0.01).[5]

4. *Postoperative Incidence of Encephalopathy*

Population A. Five of nine patients randomized for nonselective shunt developed postoperative encephalopathy compared to one of nine patients randomized for selective shunt (Population A, Tables 1–3). Incidence of encephalopathy after nonselective shunt was significantly greater (p = 0.01) than after selective shunt in the prospective randomized population (Population A, Tables 2–4).[5,14]

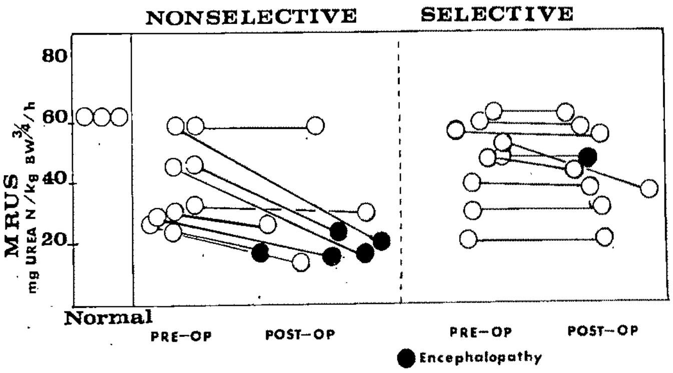

FIG. 2. A comparison of the effects of nonselective and selective shunts on the maximal rate of urea synthesis (MRUS). A significant decrease is induced by the nonselective shunt (p = 0.025) which is accompanied by a significantly greater incidence of hepatic encephalopathy (p = 0.01).

Population A plus Population B (Tables 1–4). Combining Population A (n = 18) and Population B (n = 19) demonstrates how postoperative encephalopathy is a disorder of altered nitrogen metabolism and can be correlated with MRUS (Fig. 3). Eighty-five per cent of patients with encephalopathy had MRUS values < 30 mg urea N/h/kg BW$^{3/4}$ (Fig. 3). The mean MRUS (normal 55–70 mg urea N/h/kg BW$^{3/4}$) of encephalopathic patients was 22.5 ± 3.32. Eleven of 37 patients in combined Populations A & B were encephalopathic. Ten of these 11 patients had nonselective shunt; one patient had selective shunt. As stated earlier, the possibility of undetected preclinical encephalopathy before surgery in Population B patients precludes definite conclusions. However, the implication that encephalopathy is less frequent in patients operated with selective shunt than in patients operated with nonselective shunt clearly reinforces the data obtained from analysis of Population A.

TABLE 4. *Incidence of Encephalopathy After Surgery (Population A & B)*

Patient	(Population B) Operation	MRUS	Encephalopathy
1.	NS	28	−
2.	NS	47	−
3.	NS	33	−
4.	NS	24	+
5.	NS	20	+
6.	NS	35	−
7.	NS	60	−
8.	NS	28	−
9.	NS	67	−
10.	NS	46	−
11.	NS	30	+
12.	NS	27	+
13.	NS	31	−
14.	NS	42	−
15.	NS	8	+
16.	NS	30	−
17.	NS	35	−
18.	S	39	−
19.	S	23	−

Discussion

Conventional or nonselective shunts have been extremely successful in the control of hemorrhage from gastroesophageal varices. However, severe morbidity and an acceleration in the rate of hepatic failure have cast serious doubts as to the true value of these procedures. The concept of selective shunting, in which portal venous perfusion of the liver is preserved, was developed with the hope of ameliorating the problems of hepatic encephalopathy and slowing the rate of hepatic failure.

A significant advance in the study of this problem has been the demonstration by Rudman *et al.*[10] of the close correlation between an impaired ability to synthesize urea and the development of encephalopathy. These techniques are of great importance in providing an objective method of assessment of encephalopathy and comparing the effects of the two types of shunt operation.

Figure 2 illustrates the contrast between the two types of shunt. The selective shunt was followed by little change in the MRUS test, and the only instance of encephalopathy was related to ingestion of drugs. In contrast, the nonselective shunt induced marked diminution in the MRUS ($p = 0.025$) and led to a greater incidence of encephalopathy ($p = 0.01$) (Population A, Tables 2 & 3). It is apparent from these data, that the selective shunt is clearly superior in the handling of protein catabolism. It appears likely that the factor responsible for the superiority of the selective technique is the preservation of portal venous perfusion of the liver.

Although the data are not yet sufficient for a definitive statement, it is our belief that patients with marked restriction of MRUS preoperatively will be a high risk group for postoperative encephalopathy. On the other hand, the data from patient #3, (Table 2) have shown that even patients with normal preoperative MRUS are not protected from encephalopathy following a nonselective shunt.

Important confirmatory data of the superiority of the selective shunt are provided by the prospective randomized clinical study (Table 5). The longest period of followup study is not yet three years, but the incidence of encephalopathy is already high in the nonselective group ($p = 0.04$). The high incidence of encephalopathy in the nonselective group does not support the widely held belief that interposition grafts in some manner protect against encephalopathy. The current survival figures are included but are not significantly different at this point.

TABLE 5. *Clinical Results in Total Prospective Randomized Study*

Type of Shunt	Number	Hospitalized Encephalopathy	Total Encephalopathy	Died
Selective	17	1	1	1
Non-selective	17	5	7	4

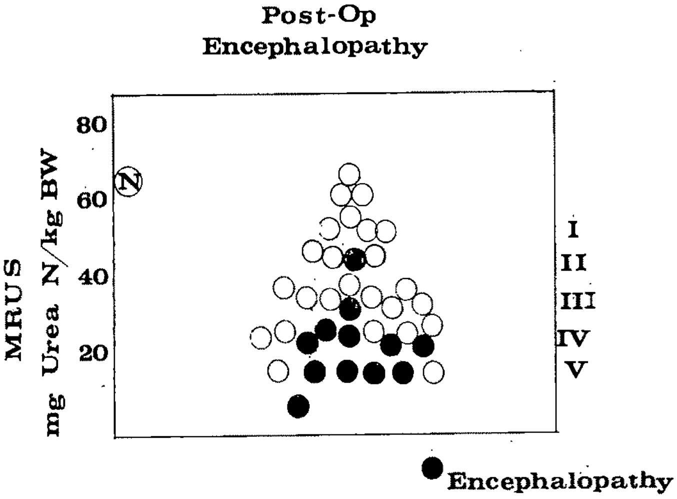

FIG. 3. Graphic demonstration of the relationship between encephalopathy and the MRUS. The encephalopathic patient with the highest MRUS was the single instance of encephalopathy following selective shunt and was secondary to utilization of sedative and analgesic medications.

Acknowledgments

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DISCUSSION

DR. ROBERT ZEPPA (Miami): I think it crucial that we appreciate the significance of this particular report, because we now have a handle for measuring—getting quantitative information—concerning encephalopathy, and I think Dr. Warren is to be congratulated.

In our own followup of the patients which he left behind and those we have added—and since he left we have added 32 patients to the present time, which brings us to a total of some 80 patients in the Miami series—of those survivors, and from 1971, the last few that he did and those we have added—we have yet to have a mortality in that group. We have yet to place a patient on protein restriction. And, as a matter of fact, most of the patients are not on salt restriction.

We brought back the long-term survivors, up to 4½ years, and tested them with the system which we had before when Dean was there in the Clinical Research Unit; that of providing the patients with a standardized protein meal and following the blood ammonia level out for several hours.

Eight of these long-term survivors were readmitted to the CRU. Six had absolutely no change in their tolerance curves over the time measured preoperatively to this long-term followup. Two, of course, did.

We consider this to fit with the information presented by Dr. Warren, although his more elegant technique will provide us with a more definitive measure of this problem.

I think that his stressing the preservation of portal venous perfusion to the liver deserves additional emphasis. Remember that in the liver unit at Sao Paulo, where they have been following 1000 schistosomal patients for some 25 years—in those patients in whom total portal diversion has been applied—that is, portacaval shunt, these patients who had previously normal arterial angiographic studies, uniformly developed at the two-year interval the arterial pattern of cirrhosis, including corkscrewing and bowing out, indicating regenerating nodules.

In this group of patients—and this information comes courtesy of Dr. Silvano Raia, who heads that unit—there is a 60% incidence of encephalopathy, which is a complication that is never seen in patients with bilharzial liver disease, because they have well maintained hepatocellular function.

DR. CHARLES W. PUTNAM (Denver, Colorado): More and more evidence has accumulated in the last several years about the profound metabolic effects of portal diversion. Furthermore, the most significant effects have been shown to be from bypassing the hormone-rich venous effluent from the upper splanchnic organs. These metabolic consequences account for the striking changes caused by portal diversion in patients with glycogen storage disease and idiopathic hyperlipidemia, as was discussed by Dr. Starzl in connection with Dr. Buchwald's paper.

The chronic splanchnic division preparation used in the Colorado laboratories has been a particularly useful one with which to discriminate the effects on the liver of nutritionally rich intestinal venous blood going to, for example, the left lobes of a dog liver, compared to the blood from the upper splanchnic organs, the hormone-rich blood, going to the right lobes. A variety of tests has shown that the two liver fragments in such a preparation live in different biochemical environments. Morphologically, the hormone-dominated right lobes have large, mitotically active and glycogen rich hepatocytes, compared to the atrophic and glycogen-depleted hepatocytes in the left lobe.

We have referred to the substances in splanchnic venous blood as being hepatotrophic. Much information, including that which I just cited, indicates that the hepatotrophic factors are mainly hormones, particularly from the pancreas.

As we all know instinctively, the Warren shunt retains hepatopetal pancreatic venous flow, at least to the extent that this existed before operation. Thus, hypothetically, the selective Warren shunt should be the best of the procedures currently available for esophageal variceal decompression.

We believe that the striking fall in the MRUS when a *non*-selective shunt is performed would probably be a reflection that this kind of shunt deprives the liver quite completely of these hepatotrophic substances.

DR. WILLIAM V. MCDERMOTT, JR. (Boston): This particular type of selective shunt has contributed enormously, not only by providing different and possibly better type of variceal decompression but also to our overall knowledge of the factors relating to encephalopathy. Obviously, the occurrence of encephalopathy relates to the type of shunt and the direct portacaval shunt has a high incidence, in the range of 20–25% in contrast to the lesser incidence (10–12%), seen after splenorenal shunts. Now these selective shunts as described by Drs. Warren and Britton, as well as the mesocaval shunt reported by Drapanas, have shown fewer post-shunt neurological complications.

However, there are other factors. Age is very important, as we all know by now. In our own series, the incidence is less than 10% in those patients shunted under 30 years of age, and then it goes up with each decade of life to a range of well over 50% in the 70s.

The hepatotropic factors Dr. Starzl and Dr. Putnam commented on this morning are relevant. Achlorhydria, or acid-reducing operations, will increase the incidence of encephalopathy, probably due to colonization of the small bowel by the urea-splitting bacteria of the large bowel.

Last, we come to the effects of alteration in liver blood flow. This is probably the most important of these factors, as has been recognized by the studies of the last few years on the hemodynamics of the liver. It is not so much the initial total liver blood flow but the effects of the shunt in altering liver blood flow which is important as Dr. Warren has emphasized. Fractionation of the total flow between the portal and the arterial circulation is certainly the significant factor. If prograde flow still exists in the portal vein, the total liver blood flow will be decreased by an ordinary portal-systemic shunt.

Now, interestingly enough, hepatocellular function, as assessed preoperatively, has relatively little to do with the incidence of encephalopathy. This brings me to a direct comment on this measurement of the maximal rate of urea synthesis, described this morning. This, I suspect, does not relate to hepatocellular function, but rather to liver blood flow. The figures shown this morning by Dr. Warren in the drop in MRUS in certain types of shunting would probably parallel decreases in liver blood flow if this had been measured simultaneously. It would be hard to visualize that the shunt would alter urea synthesis directly because there is such an enormous reserve in the Krebs-Henseleit cycle; so much so that 85 or 90% hepatic resection does not demonstrably alter the rate of urea synthesis.

So I think that this particular test reflects an alteration of liver blood flow brought about in variable degrees by the differing types of shunts. I would be interested in Dr. Warren's comments on this.

Whether this is useful as a predictor is hard to say from the data presented this morning, because it was not the rate of urea synthesis preoperatively that was the predictor, but the change that occurred as a result of the operation—exactly the situation we find in liver blood flow.

This type of shunt probably is not effective in patients who have a high degree of postsinusoidal block and refractory ascites, and who also need a shunt for decompression of varices. But, interestingly enough, it's this group of patients who probably would not have much change in liver blood flow as a result of one of the older shunts. Thus, this type of selective shunt is applicable to a certain group of patients with portal hypertension, but, I think, not to all of them.

DR. CLARENCE DENNIS (Bethesda): Dr. R. Janis Adamson, my associate at Downstate was much impressed with the importance of maintaining a satisfactory head of pressure in the hepatic portion of the portal vein, in the interest of having no change in the perfusion of the liver from this source as a result of doing shunts. He did a straightforward end-to-side portacaval shunt, reopened the umbilical vein, and did an anastomosis of the gastroepiploic artery to the reopened umbilical vein, of such size as to maintain the same pressure in the proximal, or hepatic, side of the divided portal vein as had existed heretofore.

As a result, patients who had been having trouble with coma and such difficulties have gone without it in the postoperative period. It was a series of seven or eight patients. It was possible to hear the arteriovenous shunt with a stethoscope. One patient went for three months with this shunt audible, and it stopped; it occluded. The patient went into coma within 48 hours.

It seems this is a second bit of evidence that the important item is to maintain satisfactory flow through the liver from the portal source. The protein tolerance curves are very much better with these than they are with the straightforward shunt.

DR. W. DEAN WARREN (Closing discussion): Dr. Zeppa's protein tolerance data is very important, because it is the only data of its kind. It's very encouraging; I would have guessed that there would have been a greater change, because of additional collateralization over the years to the low-pressure splenic system. But it's very encouraging to have that data. Also, I think his comments about the schistosomiasis study are extremely important, as that study presents such a conclusive bit of physiologic evidence.

Dr. Putnam gave an excellent discussion, and we are great admirers of the work that he and his young associate, Dr. Starzl, have done. Their work has contributed significantly to our conviction that portal perfusion of the liver would be significantly beneficial to the patient.

Dr. McDermott, who started all of this some years ago with his studies of ammonia and "episodic stupor," has certainly been one of the most productive men in this field over the years.

I would like to correct him on one thing, however, his statement that mesocaval shunts carry a lower incidence of encephalopathy. The shunt we were randomizing against is mesocaval, or mesorenal (which is the same thing on the left side) and this approach has been accompanied by a high incidence of encephalopathy. Although the study is not yet three years old, there are seven out of 17 interposition shunts with clearcut encephalopathy.

I think he's right about the various factors influencing encephalopathy, such as age. Dr. Zeppa told me that the oldest patient to maintain the early level of protein tolerance of our original group is now 74. Our mean shunt age, my associate, Dr. Millikan, tells me, is 52. Sheila Sherlock advises against portacaval shunts in patients over 50; so you can see that with the selective shunt one need not fear age to the same degree.

I think Dr. McDermott is right in his assessment of the importance of hepatic blood flow. As you know, I have felt this for years, and have been greatly frustrated by the lack of definitive techniques to measure total hepatic flow, hepatic arterial flow, and portal venous flow. Such data are greatly needed. The MRUS does not correlate well with conventional hepatic function tests. It adds additional and important data to our preoperative studies. I believe it will be of significant prognostic value; it appears that patients with severe restriction of urea synthesis preoperatively are much more likely to develop postoperative encephalopathy. On the other hand, a high MRUS does not give assurance of protection against encephalopathy from a total shunt. This is the point I think you were making.

Dr. Dennis' comments about the arterialization patients of Dr. Adamsons, I think, are very apropos. I believe that arterialization is somewhat better than a total shunt by itself. It suffers from the fact that the hepatotropic factors in portal blood, whatever they are,—are not as effective if they have circulated through the systemic circulation. Secondly, the arterialization procedures have carried a high incidence of late occlusion.

Peritoneo-Venous Shunting for Ascites

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A new minor surgical procedure for ascites has been devised wherein a specially designated one way pressure activated valve is implanted to create a permanent peritoneo-venous shunt. The normally closed valves opens only when the peritoneal pressure rises 3–5 cm higher than the intrathoracic venous pressure thus preventing backflow of blood and closing the valve should the venous pressure rise from the over-infusion of ascitic fluid. The procedure has been performed on 45 patients but nine were terminal at the time of surgery. Prolonged relief of ascites occurred in 28 of 37 cases.

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ASCITES is a disease which is caused by obstruction to the hepatic venous outflow tract with resultant increased filtration of fluid from the vascular compartment. This is most certainly a mechanical problem; and logic tells us that diseases which have a mechanical basis are best treated surgically while diseases which are biochemical in nature respond more favorably to medicine. Since surgeons are preoccupied with the operation of portacaval shunt, internists are inclined to treat this disease medically and withhold surgery as a last resort in end stage disease.

The salient pathophysiology of ascites due to cirrhosis is the increased formation of fluid in the peritoneal cavity. This fluid formation obeys the principles set down by Starling. Equilibrium is reached with a tense intra-abdominal hydrostatic fluid pressure. At equilibrium, the colloid osmotic pressure of the serum minus the colloid osmotic pressure of the ascitic fluid is equal to the portal capillary pressure minus the intra-abdominal hydrostatic pressure. Most of the fluid is filtered from the surface of the liver, but the visceral peritoneum makes a significant contribution. Liver capillaries are permeable to protein otherwise plasmsa proteins synthesized by the liver could not gain access to the circulation. This circumstance accounts for the high concentration of protein found in ascitic fluid, and impedes the reabsorption of fluid from the peritoneal cavity. Sherlock[1] has found that serum osmotic pressure is considerably reduced in cirrhotics with ascites.

Internists have concentrated their attack on salt metabolism, although there is some doubt whether renal handling of sodium in cirrhosis is abnormal. When the interstitial fluid requirement is satisfied, the injection of sodium chloride into patients with ascites is followed by naturesis.[7]

Salt intake does play an important role in the formation of ascites just as it does in the formation of peripheral edema in the hypoproteinemia of malnutrition. Salt loading not only favors retention of extracellular fluid in normals but accentuates the collection of extracellular fluid in areas of predilection secondary to venous obstruction such as the lung in left heart failure and the extremities in right heart failure, or the abdomen in ascites. Sodium excretion in the urine is sharply diminished during the formation of edema or ascites. Medical therapy therefore must decrease the effective, extracellular fluid volume before it influences the removal of extracellular fluid in areas of predilection. Iatrogenic reduction in the extracellular fluid volume may be the stimulus for the increased absorption of sodium by the renal tubules.

The development of potent diuretics has given the internists an opportunity to intensify the treatment of cirrhotics. As a consequence, most medically treated patients had become hyponatremic, oliguric, hypovolemic and axotemic before they were referred to surgery. Some patients were so depleted that they had

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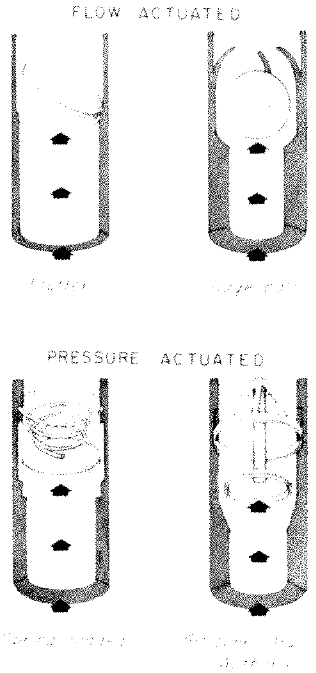

Fig. 1. Schematic depicting the operating principles and types of one way valves with respect to their mechanisms of closure.

become hypotensive. In a recent study,[2] 34 of 48 cirrhotics with ascites had significant renal failure at death with a strong iatrogenic etiology.

Not only is diuretic therapy and salt restriction unphysiologic, it makes health an unattainable goal for cirrhotics with ascites.

Why not restore the filtered plasma which has become ascitic fluid back to the circulatory system from whence it arose? There is a good deal of accumulated literature which shows that infused ascitic fluid causes diuresis and naturesis,[9] restores patients vigor,[3] and is generally favorable to renal function.[5]

It is little wonder, therefore, that surgeons have attempted the continuous reinfused of ascites to the venous system by a peritoneo-venous shunt.[4,6,8] Still, the published results are few and inconclusive. Only one long term followup is available. Surgeons have invested too little time and effort into defining and solving the problems of peritoneo-venous shunt which might transform the procedure from an idea of promise to a surgical practicality. "Off the shelf" valves, available for the treatment of hydrocephalus have been selected without basic consideration for the hydrodynamic requirements. The technique of surgery and the hydrodynamic requirements involved in the successful transport of this

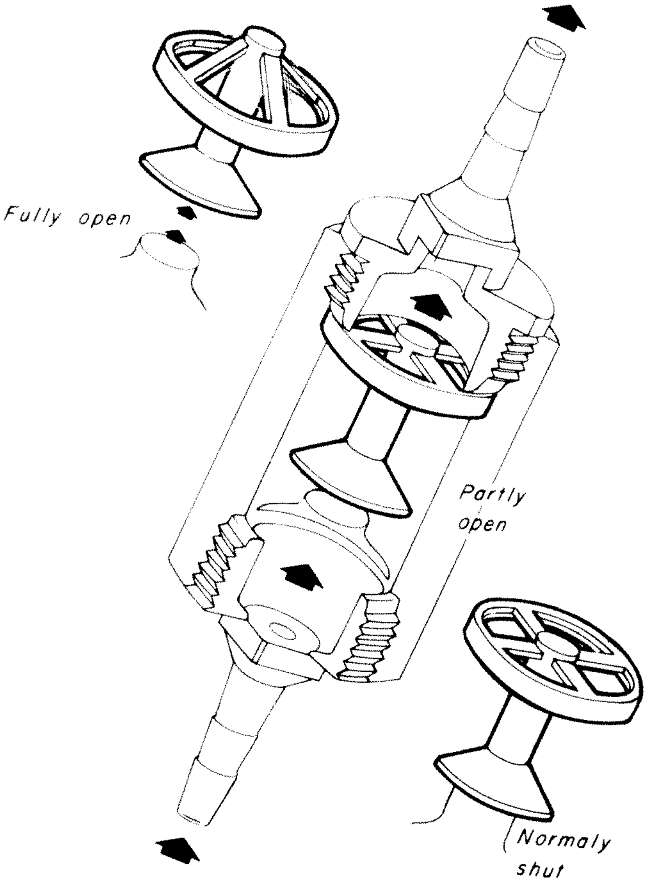

Fig. 2. Construction of the valve used by the authors. The valve is held in the normally closed position by tension on the silicone rubber struts.

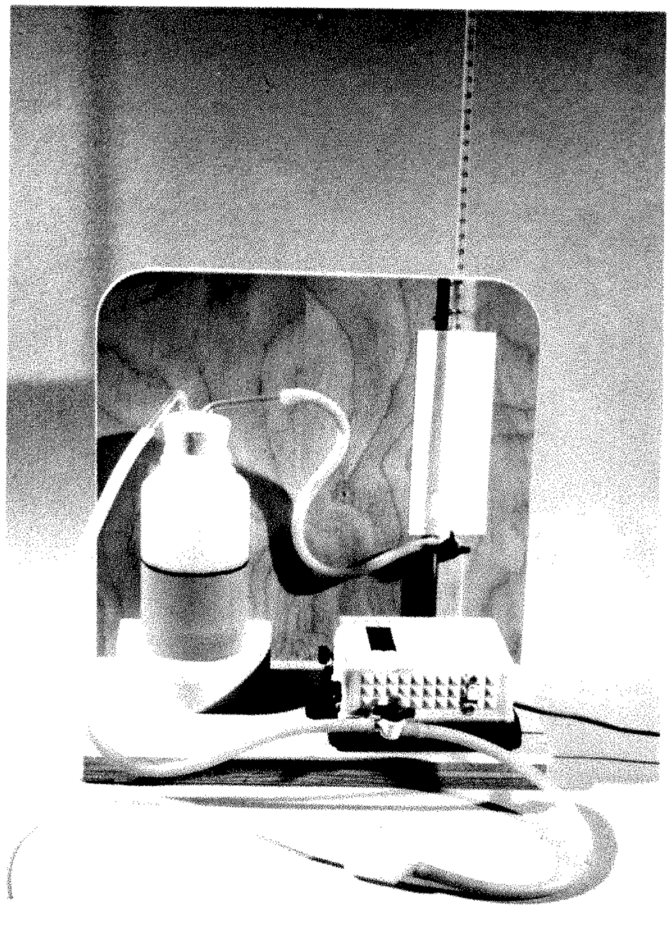

Fig. 3. Valve function is examined manometrically. Opening pressure and competence at low pressures are important characteristics.

fluid both require study. These aspects of the problem prompted our investigations in animals and humans.

Experimental

The exact details of valve requirements were worked out by *in vitro* hydrodynamic studies and dog experiments which will be merely summarized here and published elsewhere.

Valves may be considered to be of two types: flow actuated and pressure actuated (Fig. 1). Flow actuated valves require a slight reversal of flow to seat a ball or a leaflet over a restricting orifice. Valve closure requires a minimum rate of flow to mechanically move the leaflet or ball. At very low flow rates, such flow activated valves become incompetent. Reverse flow even occurs in the saphenous veins at low pressure differentials. This slight regurgitation of blood at low pressures may cause the displacement of only 2 or 3 cm^3 of blood, hardly sufficient to be called serious back bleeding; but, the blood which enters the tube is now contacting a thrombogenic surface and clotting promptly ensues, thus occluding the lumen.

Varying types of valves were tested in dogs rendered ascitic by caval ligation. Flow sensitive valves failed when most of the ascitic fluid had been drained and the venous and peritoneal pressure differences approached one another.

Since the inside surface of the silicone rubber tubing must always look at ascitic fluid rather than blood, reversed flow is not tolerable. This can be prevented with a pressure sensitive valve. Since no satisfactory valve was available, a new design was undertaken. For theoretical considerations, the pressure activated valve should have a critical opening pressure of 2-5 cm of water. The design of a valve with such sensitivity seemed impossible; but, by using the tension created by small silicone struts a suitable valve was developed (Fig. 2).[*] The body of the valve is made of non reactive polypropylene and the diaphragm valve with its attached silicone struts is made of a low durometer silicone elastomer. This valve was bench tested *in vitro* (Fig. 3). The critical opening pressure was consistantly between 3 and 5 cm of water, and leakage did not occur.

This valve design was tested in 6 dogs rendered ascitic by ligation of the vena cava cephalad to the entrance of the hepatic veins. The valve and the perforated collecting tube were placed in the peritoneal cavity through a small abdominal incision. The solid silicone venous tubing was drawn through a subcutaneous tunnel into the neck where it was inserted into the internal jugular vein through a venotomy. The tube was cut so it extended into the superior vena cava. The appearance of a preoperative and two month postoperative dog is shown in Fig. 4 together with a schematic diagram of this shunt. The valve remained patent in experimental dogs for over three months at which time the animals were destroyed.

The critical opening pressure of 3-5 cm of water was chosen to prevent blood from regurgitating into the silicone rubber tubing and at the same time to take

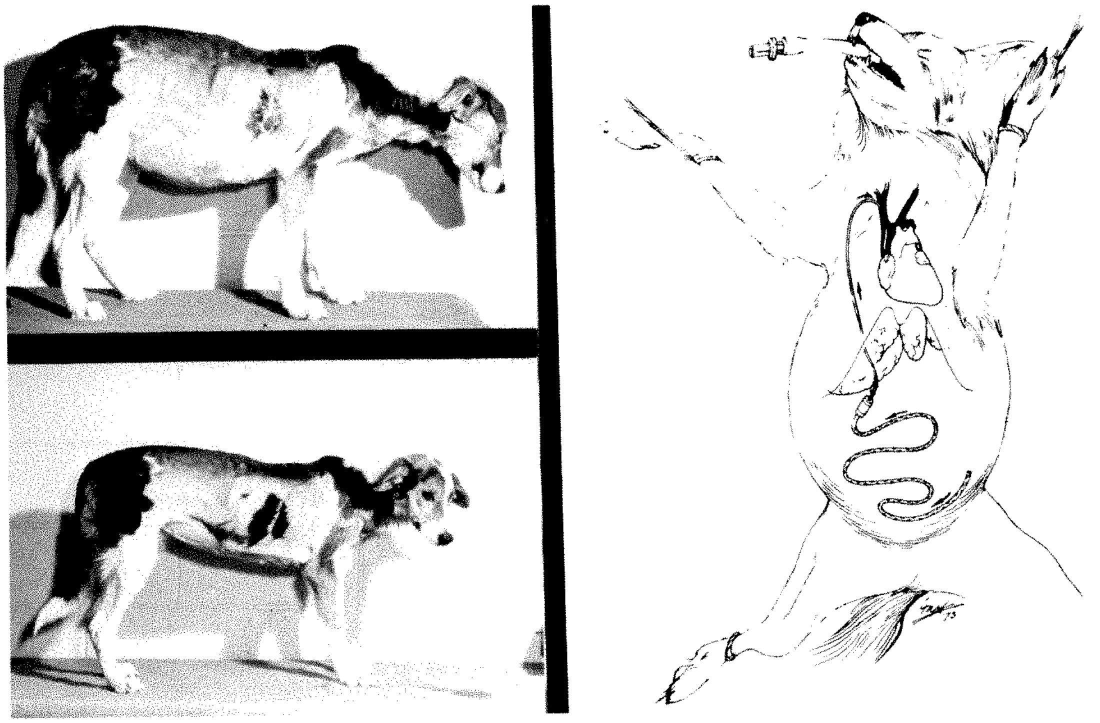

FIG. 4. An ascitic dog is shown prior to peritoneo venous shunt and two months after surgery. The diagram illustrates the placement of the valve system. Alleviation of ascites and gain in muscle mass attests the success of the surgery.

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[*] Valve available on experimental basis from Dr. LeVeen.

advantage of the pumping action of respiration. As the diaphragm descends during respiration, the intra-thoracic pressure falls and the intra-abdominal pressure rises. This produces a pressure differential sufficient to empty the ascitic fluid into the vena cava in ascitic animals and humans. In the reclining position the differential pressure changes between the peritoneum and the superior vena cava are shown in Fig. 5 during normal respiration, forced deep respirations, inspiring against resistance and expiring against resistance. Notice that at the peak of inspiration the peritoneal pressure exceeds 5 cm of water allowing ascitic fluid to open the valve. Forced deep respirations exaggerate the normal excursions and bring the differential pressure between the peritoneum and the vena cava far above 5 cm with each respiration. Inspiration against resistance of 5 cm of water is very effective in widening the differential between the caval and peritoneal pressure and can be used clinically to hasten the emptying of ascitic fluid into the venous system. On the other hand, expiration against resistance or intermittent positive pressure breathing leads to closure of the valve. Insertion of a pressure sensitive valve with a critical opening pressure introduces a new homeostatic mechanism which prevents overinfusion. As more fluid is pumped into the venous system, the venous pressure rises. Overinfusion is not possible since a significant rise in venous pressure closes the valve and protects against heart failure and pulmonary edema. Therefore, it is unnecessary to monitor central venous pressure after introduction of the valve.

Clinical Experience

Techniques—Management

Most procedures were done under local anesthesia. A transverse incision 2–3 inches in length is made in the abdomen medial to the anterior axillar line lateral to the rectus sheath and below the liver edge. The abdominal muscles are split. If the ascites is tense, a small amount of fluid may be allowed to escape; but the loss is kept to a minimum by traction on sutures placed prior to opening peritoneum. These sutures are used to pull the peritoneal edges together. After the peritoneum is opened, the valve and its perforated tubing are quickly inserted into the abdominal cavity, and the peritoneum closed around the stem of the valve or the tubing. Closure of the muscles and anterior rectus sheath prevents leakage of peritoneal fluid from the wound. Gentamicin solution (40 mg in 100 cc saline) is instilled in the wound during closure. A long tunneling instrument is pushed subcutaneously from the abdominal wound toward the neck. This procedure may not require local anesthesia in a well-sedated patient. A transverse incision 1½ fingers above the clavicle exposes either the external or internal jugular veins. Local anesthesia and incision of fascia over the clavicle is almost always necessary to complete the subcutaneous tunnel without pain. A long heavy silk tie is drawn through the tunnel to the abdominal wound.

The venous tubing is doubled at its end and tied to form a loop. The silk suture from the neck is tied into this loop. The tubing is then pulled into the neck wound. A venotomy site is chosen either in the internal or external jugular. The distance from the venotomy site to the 2nd interspace is measured with the venous tubing and the excess is trimmed. A longitudinal venotomy is made between two 5–0 traction sutures. The vein is tied above with a ligature and a ligature below is tied after insertion of the tubing. If any obstruction to the passage of the full length of tube is encountered in the external jugular, the tube should be appropriately shortened or

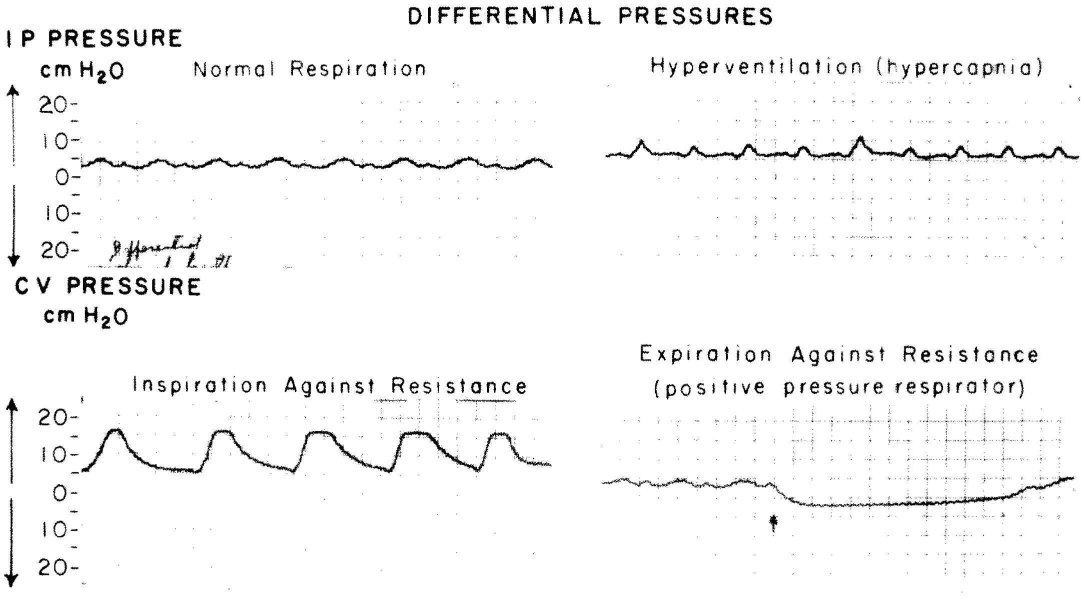

FIG. 5. Recordings demonstrating pressure changes between peritoneal cavity and superior vena cava during normal respiration, hyperventilation, inspiration and expiration against resistance. Note the large pressure gradient which develops with inspiratory resistance.

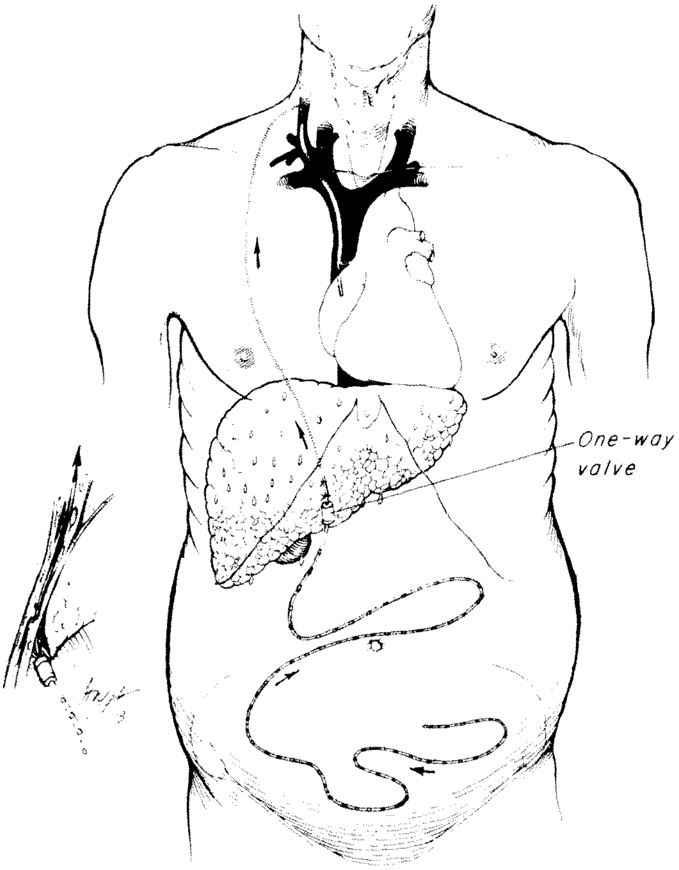

Fig. 6. The phantom view illustrates the placement of the valve and collecting tube in the peritoneal cavity and the venous tube in the superior vena cava in the completed operation.

placed in the internal jugular. The completed operation is shown in Fig. 6.

If the abdomen in tense, external compression is avoided for the first 12–24 hours. Thereafter, an external

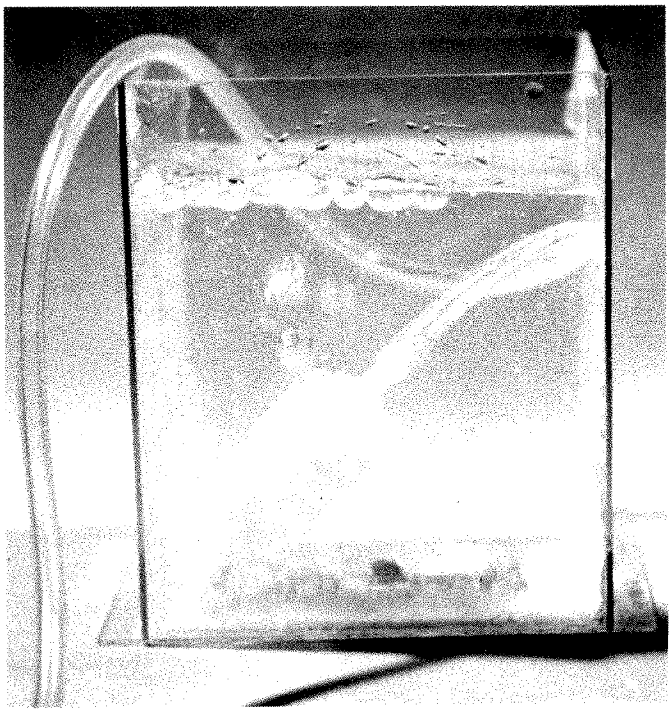

Fig. 8. The leak along the threads developed after sterilization and was not detected until valve failure had occurred.

elastic binder is affixed. After 24–48 hours, the patient is started on respiratory exercises which consist of inspiring through a tube against resistance of 5 cm of water (Fig. 7). This breathing exercise is done in the reclining position. It is continued postoperatively for 15 minutes 4 times a day, to take advantage of the pumping action created by the negative intrathoracic pressure. Patients with thinned and stretched abdominal walls will not mobilize all of the ascitic fluid without respiratory exercises. They will merely overflow from a large residual 3rd space. Eliminating all of the ascites takes the

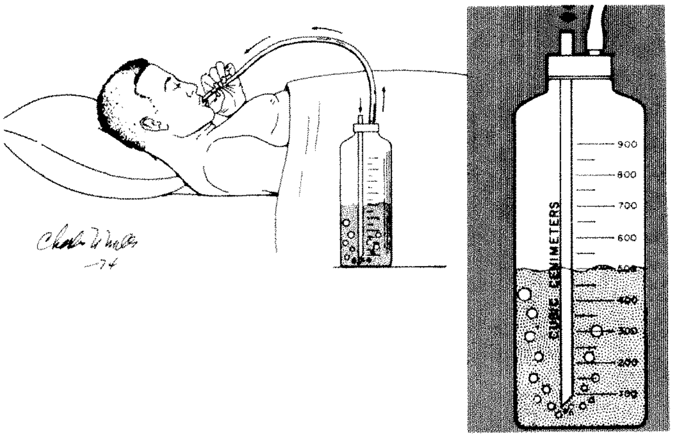

Fig. 7. The patient inspires against resistance of about 5 cm of water to increase the differential pressure between the superior vena cava and the peritoneum.

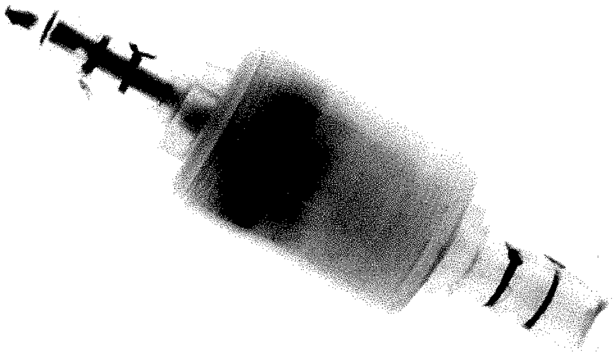

Fig. 9. The leakage along the threads allowed blood to displace ascitic fluid in clot forms down to the valve but the valve is competent and blood is kept from extending below the valve.

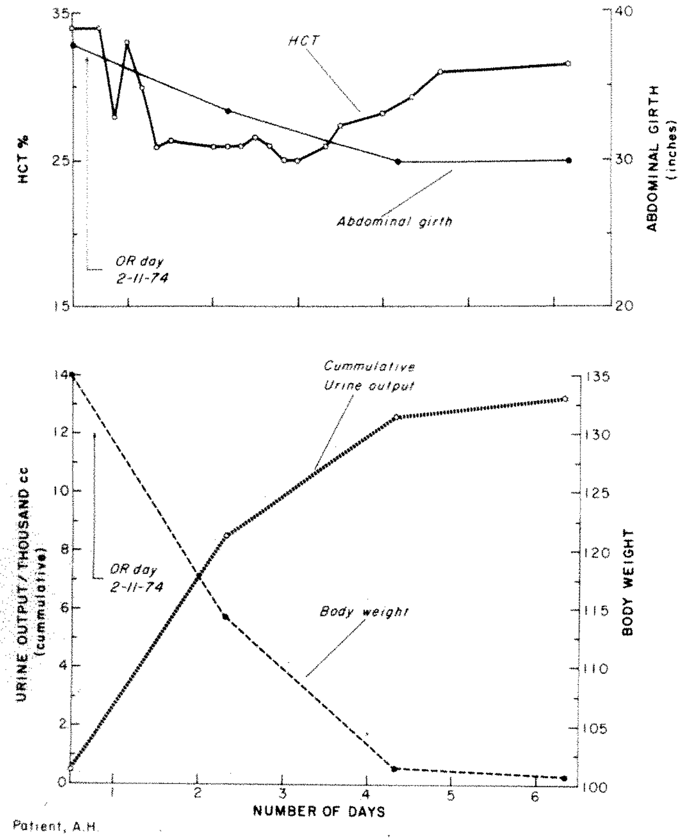

FIG. 10. The hematocrit drops precipitously as the girth circumference decreases. It remains low until the third day when the body weight stabilizes and urinary output tapers off after a weight loss of 30 pounds. The failure of the hematocrit to reach normal indicates a deficiency in the red cell mass. The appearance of the patient is shown in Fig. 16.

cooperation of the patient in performing the respiratory exercises three or four times daily for 10–15 minutes.

Results

The patient series consists of 19 cases personally operated upon and studied and 26 patients operated upon by other surgeons who generously supplied their patient data. Some of these patients were jaundiced and were at the end stage of liver disease and expired within the first week after valve insertion, although one patient survived a month, this accounted for five deaths. Jaundiced patients in liver failure cannot be helped sufficiently by valve insertion. Six patients were anuric or oliguric when transferred to surgery. Two of the six were hypotensive, four of these six patients failed to respond with an increased urinary output and died in renal failure. One of these patients had cardiomyopathy and the venous pressure rose without augumenting the cardiac output or the urinary excretion. Two patients responded with increased cardiac output increased urinary output and survived to lose their ascites. One of these desperately ill patients has lost his ascites, improved his renal function and is now enjoying restored health. This experience has led us to reject patients for surgery if volume expansion with plasma or blood combined with furosamide does not bring about an increase in urinary output. This has left 13 patients in our series and twenty one patients from the outside series for extended observation. Two patients succumbed from bleeding varices after successful treatment for ascites, both patients are considered successes with respect to the ascites treatment.

Failures

Two patients, one in our series and one in the outside group, developed infections and required removal of their shunts 2½ weeks postoperatively. Both patients had recovered from their ascites in the interim and in spite of the removal of the tube were physically improved and more easily managed. In one patient, the ascites did not reappear. In our patient, prophylactic antibiotics had

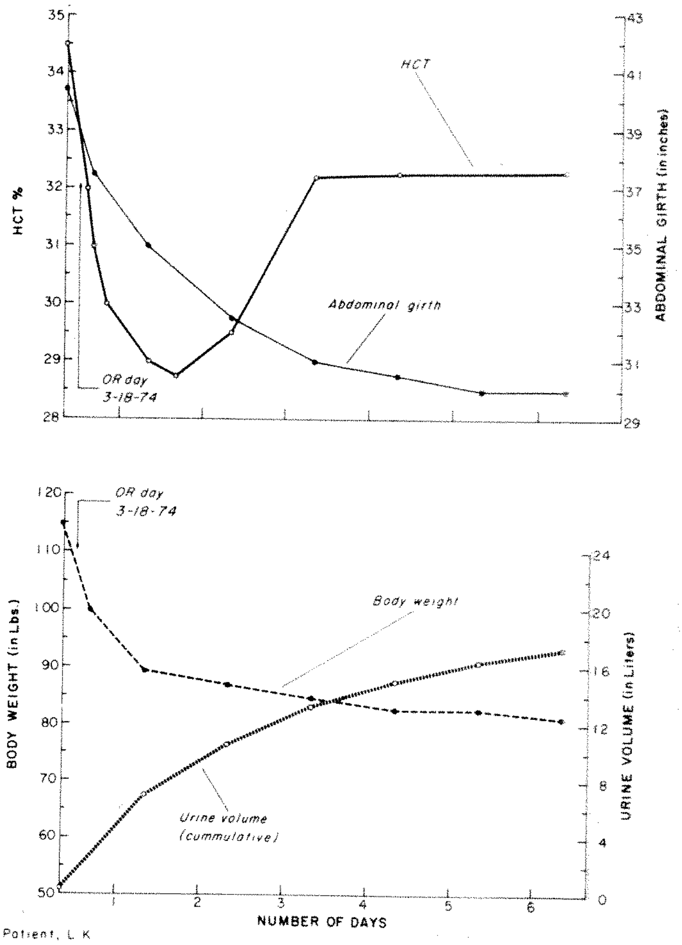

FIG. 11. The patient is a double amputee with ascites. Placement of the valve produces a hemodilution lasting for four days. Notice that the hematocrit never returns to normal indicating a true red cell deficit. The patients appearance is shown in Fig. 15.

been inadvertently omitted. One third of the shunts became occluded usually 1–2 weeks postoperatively after the ascites had been completely disappeared. The sudden reappearance of ascites heralds an occlusion of the shunt. All removed valves were examined to ascertain the cause for failure. Ninety per cent of the failures were produced by leakage of ascitic fluid around the threads of the valve allowing blood to replace the ascitic fluid in the venous tubing (Figs. 8, 9). This defect has now been corrected by sealing the threads. This blockage can easily be flushed from the venous tube and the valve replaced. It was unnecessary to replace the venous tube in any. Two patients required two replacements of the valve. In one case failure occurred after three months. Nevertheless, shunts which are patent longer than one month usually remain patent.

Correction of the defects in the valve should reduce occlusion rate to about 5%. Occlusion of the shunt was due to thrombosis in the venous tube due to a faulty valve system in all but one instance. Occlusion of the shunt produces only temporary failure and requires prompt valve replacement. Permanent failure was encountered in one patient with tricuspid insufficiency with such a high venous pressure that the valve would not open. One patient with a huge hepatoma and ascites responded favorably for two months but seemed to do less well during the last two months of his life, although no definite evidence of either tube blockage or excessive ascitic fluid was confirmed to us. The result was considered satisfactory by his surgeon.

Clinical Success

Thirteen patients in our series after one or more valve insertions have been followed for one week to 1½ years with relief of ascites. Five are more than six months with ascites relieved although one required a valve change in this interval. Twenty-one outside cases on whom information is available have lost their ascites from two weeks to six months. Six have occluded and have not been replaced with the new sealed valves, although three patients have had one or more valve replacements.

The postoperative weight loss averaged about 14 pounds per day with the loss accountable in the excretion of urine. Most patients lose at least 50 pounds of liquid. The hematocrit falls immediately after surgery due to hemodilution. The reduction in abdominal girth indicates that hemodilution is occurring (Figs. 10, 11). As urinary loss continues and ascites diminishes, the hematocrit returns toward normal but never reaches the preoperative level indicating that these patients are depleted of red cell mass. The red cell deficit is always more severe than realized and transfusions of packed cells may be necessary lest the hematocrit fall too low during the period of hemodilution (Fig. 12). The largest urinary loss in a single day has been 13 L. Such a diuresis

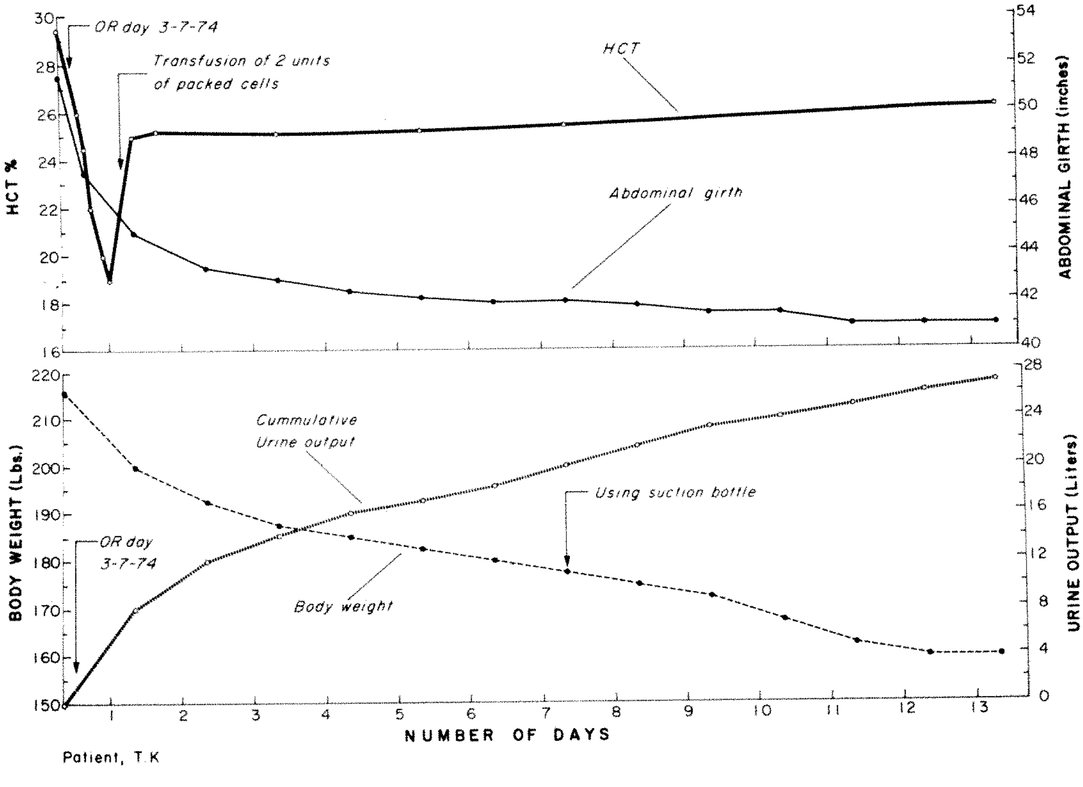

FIG. 12. The drop in the hematocrit was serious enough in this patient to require transfusion of packed red cells. In spite of these transfusions there is still a deficiency in the red cell mass. A weight loss of 58 pounds of ascitic fluid occurred. The patients physical appearance is shown in Fig. 14.

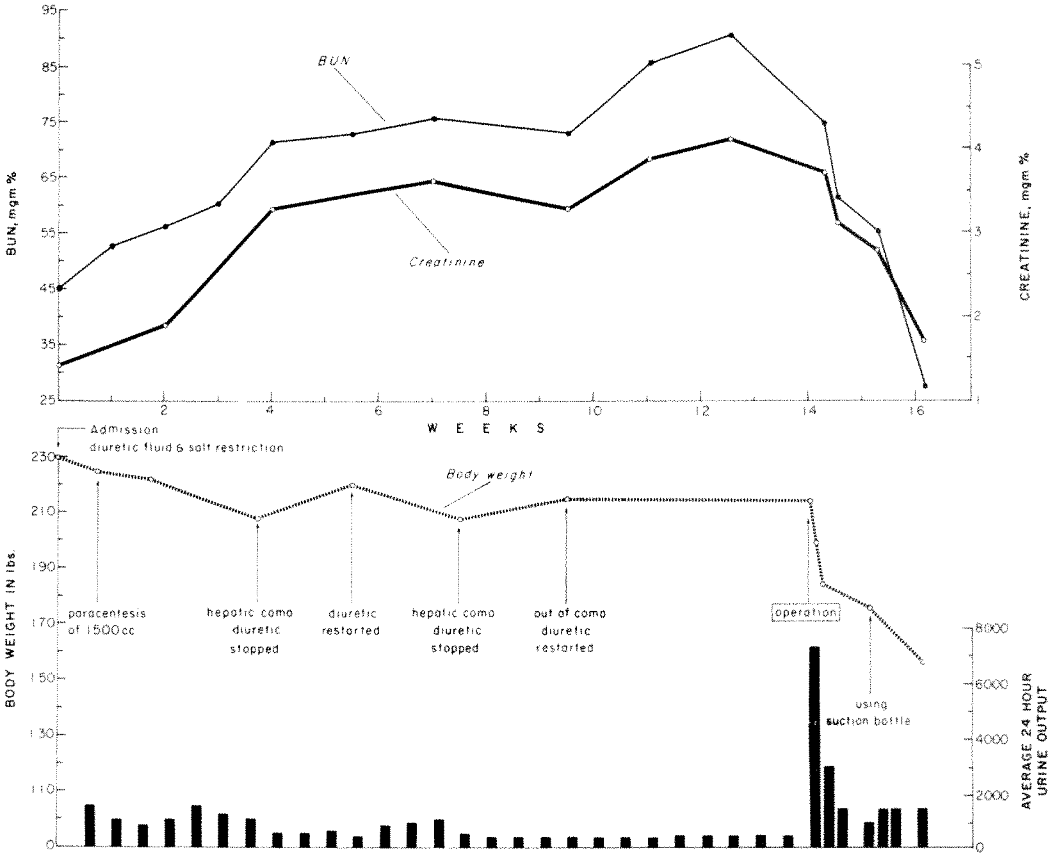

FIG. 13. The hospital course of a patient is charted. Notice that strict medical therapy and paracentesis produced only a 10 pound weight loss. Each time diuretics were tried the patient lapsed into coma with persistent oliguria. Finally, a peritoneo-venous shunt resulted in the loss of 58 pounds of fluid and a drop in the blood urea nitrogen and restoration of health and comfort. The course is that of patient shown in Fig. 14.

may be accompanied by a fall in serum potassium sufficient to require I.V. replacement therapy. Parenteral furosamide is given in 40 mg doses around the clock for the first 48 hours to maintain a maximal urinary volume. Later, the dosage is given orally. By the end of the first 10 days, the requirements for furosamide may decrease to once or twice a week or none at all. The excessive use of salt in food is avoided, but salt intake is not restricted.

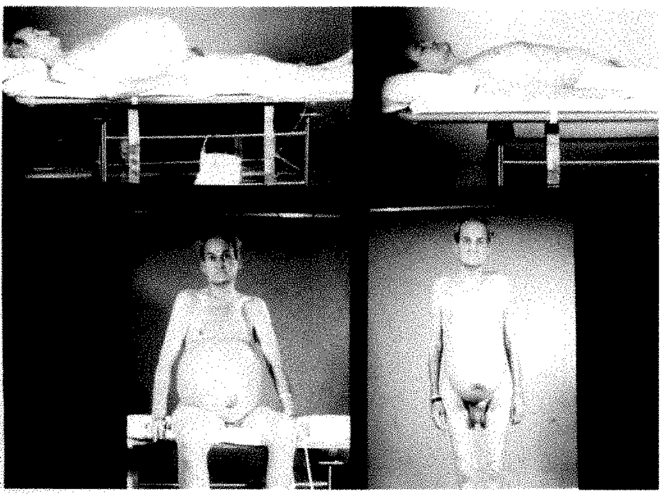

FIG. 14. The before and after appearance of the patient whose course is charted in Figs. 12 and 13. The patient was unable to stand preoperatively. Probably because the high B.U.N. raised his blood ammonia levels sufficiently to cause ataxia.

The usual hospital course of a patient with severe ascites is charted in Fig. 13. The admission weight was 230 pounds. Rigorous therapy consisting of paracentesis (1500 cc) salt restriction, and diuretics brought about a loss of 20 pounds with an associated rise in the B.U.N. and the induction of hepatic coma requiring the abandonment of therapy. The patient emerged from coma and restored 10 pounds to his body weight. Diuretics

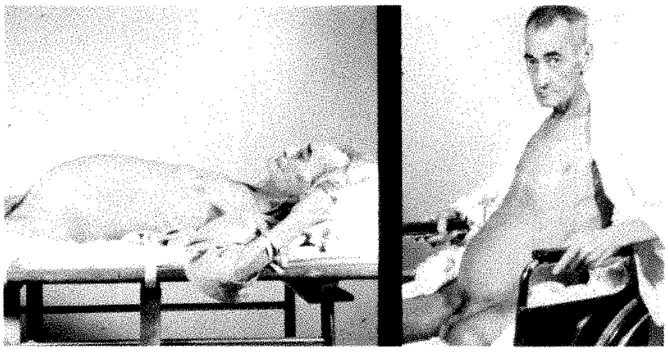

FIG. 15. The patient is a double amputee with cirrhosis. His first valve clotted after three months and was replaced with a valve which has remained patent.

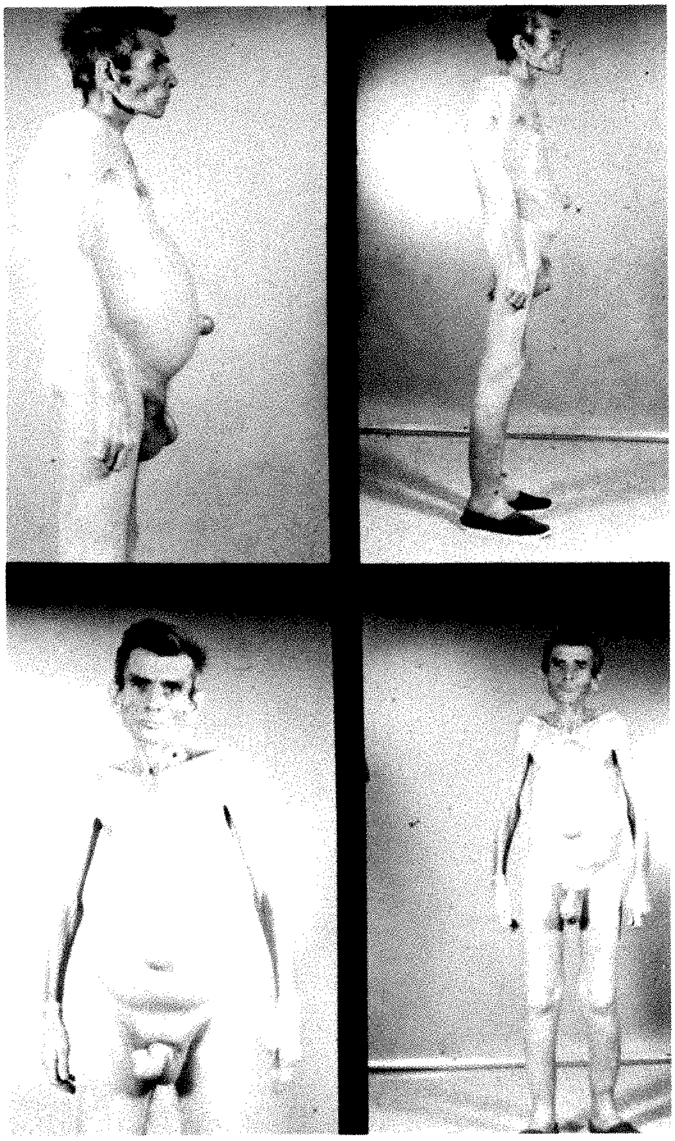

FIG. 16. The tense abdominal ascites and the usual thin walled umbilical hernia is shown. One must guard against the entrance of air into the peritoneal cavity on the subsequent repair.

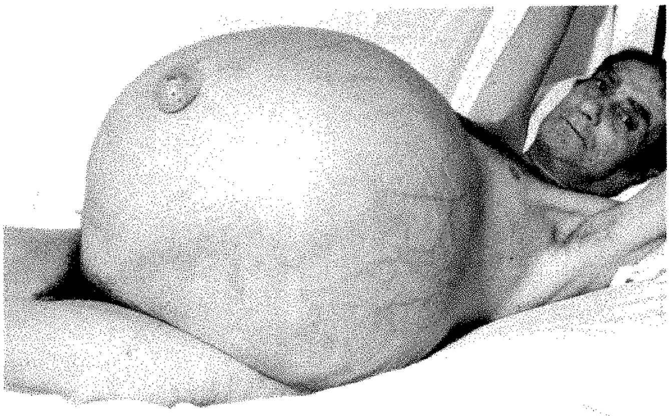

FIG. 17a. This patient had such tense ascites that he could not stand and could only breath if lying on his side. The valve has been functional for 1½ years, but the patient is uncooperative about his breathing exercises and always carried residual fluid until a second valve was inserted.

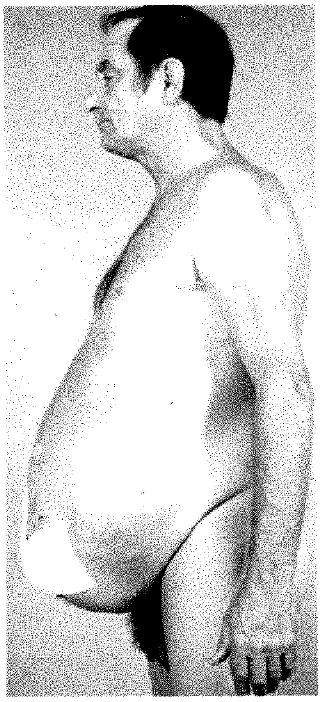

FIG. 17b. Appearance of patient in Fig. 17a, 1½ years later shows the residual ascitic fluid. The valve has been inspected to verify its patency and function. Since a second valve insertion the abdomen has become and remained flat.

were reinstated which again thrust the patient into hepatic coma. Thereafter, the patient maintained his weight at 217 pounds but after 14 weeks of therapy his renal function was failing. He became hypotensive and the average daily urinary output dropped to 20 cc per hour. The placement of a peritoneo venous shunt resulted in a weight loss of 55 pounds within the week. The B.U.N. has returned to normal and remained there. The patient was discharged two weeks post surgery without ascites and without dietary restriction or diuretics.

The typical appearance of patients before and after operations are shown in Figs. 14–18. Notice not only the loss of ascitic fluid, but the rapid loss of the cirrhotic facies with the restoration of muscle mass and fat. The facies begin to change within weeks after surgery Figs. 19, 20. Most impressive is the immediate sense of well being and return of appetite and strength. This is accompanied by a weight gain without the recurrence of ascites.

Excluding immediate deaths from end stage disease, and infections in whom the valves were removed, a total of 34 cases remain for analysis. Seven cases originally lost their ascites but the shunts have clotted and the valves were not replaced. These patients could be converted to successes. All but the patient with tricuspid insufficiency of the remaining 27 cases were successful. Nevertheless, the procedure was successful in 26 of 34 cases.

Discussion

Plasma proteins have risen to normal following shunting with a return of the albumin globulin ratio toward normal. Of special interest has been the improvement in kidney function following peritoneo-venous shunts. This has not only been accompanied by an increased urinary output but by a higher concentration of urea in the excreted urine. Elevated blood urea nitrogen falls rapidly to normal and remains in the normal range. This is of special interest since medical therapy tends to precipitate renal failure.

It is essential that the surgeon not try to combine medical therapy with peritoneo-venous shunt. All that could possibly be accomplished with diuretics then would be a dimunition in the rate at which ascitic fluid is formed by filtration. A reduction in this rate may not be desirable since it would reduce the amount of fluid flow through the shunt. A reduced fluid flow might precipitate clotting in the silicone tubing. Diuretics should be reserved for the treatment of peripheral or pulmonary edema and not be used to compete with the shunt in the reduction of ascitic fluid.

The same reasoning applied to the use of salt. Our inclination is not to restrict salt.

Obviously, renal function and the handling of salt and water require future studies in shunted patients.

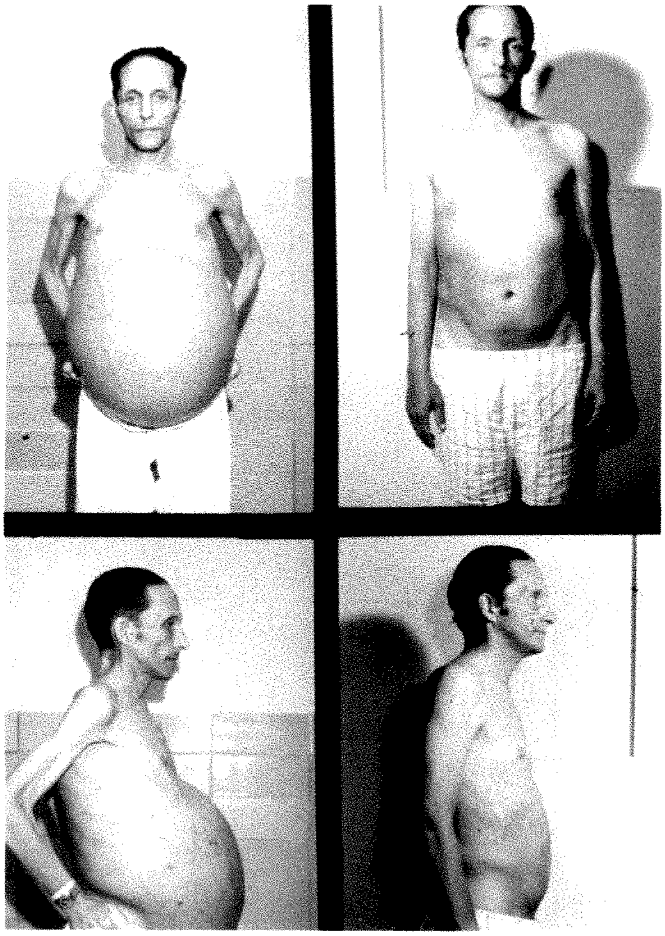

FIG. 18. A patient approaching terminal wasting ascites is shown before valve placement and 8 months later.

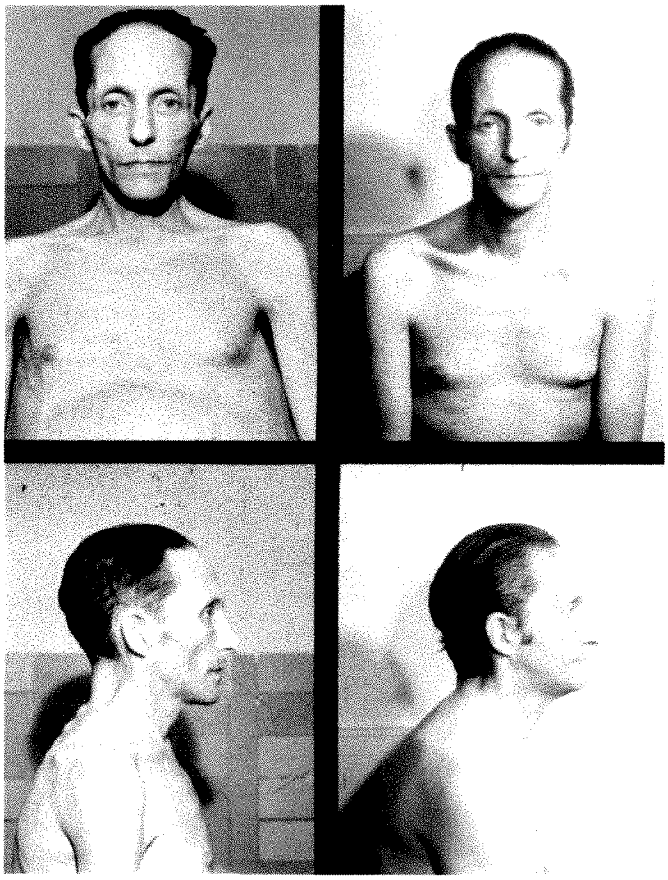

FIG. 19. The postoperative facies of the patient in Fig. 18 shows the loss of the so-called cirrhotic facies.

The operation is simple and can be performed with little or no trauma or blood loss. The results are gratifying and long-lasting. Most important, the patient no longer thinks of health as a non-attainable goal. Many of the patients suffered sufficiently to condition themselves negatively to the use of alcohol, but a few have gone back to heavy drinking and have returned with jaundice and hepatic decompensation.

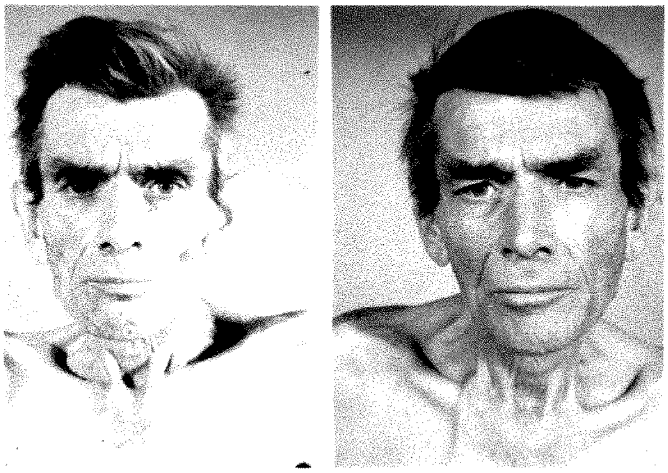

FIG. 20. The rapid change in facies is shown in photographs taken 3½ weeks following surgery.

One patient hemorrhaged from esophageal varices and developed ascites after a disconnection operation with sclerosis of the varices. This patient then was successfully treated with a peritoneo venous shunt and has been well for six months. However, patients who develop bleeding after a peritoneo venous shunt are not so fortunate. They cannot have a laparotomy without interrupting the peritoneo venous shunt, otherwise the air which enters the abdomen at laparotomy would be transported to the venous system and produce fatal air emboli.

One patient who was being dialyzed for chronic renal failure developed ascites. The ascitic fluid developed a uriniferous odor and the peritoneum became thickened. The ascites impeded the effectiveness of the dialysis. This patient has had a peritoneo venous shunt and is now being successfully managed by dialysis.

Thrombosis of the shunt has been a problem, but each time a correctable defect has been encountered. With the new modifications in the valve system, the thrombosis rate should decrease to about 5%. If this should not be realized it may be wise to consider the subcutaneous implantation of a flushing system which will clear the valve and the venous tubing. Only subsequent experience will determine whether modifications are necessary.

Although thrombosis of the tubing is sometimes difficult to detect, the use of radioactive isotopes has been of value to show tubal patency.

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DISCUSSION

DR. WILLIAM RHOADS WADDELL (Denver, Colorado): I'm speaking for a small group of surgeons in Denver and surroundings who have been evaluating a similar type of approach with an adaptation of a valve designed by an engineer at Denver University named John Newkirk. He designed this valve for the neurosurgeons, and it has had extensive use throughout the world for the treatment of internal hydrocephalus.

Originally, one of the attractive features of it was that the whole thing costs less than $10, but now it's up to $65, and the valve I'm speaking about is even worse. It costs $150.

The concept of the valve mechanism is somewhat different from that described by Dr. LeVeen, and I will show it to you now. (Slide) This is the whole apparatus. This is a chamber which is placed over the iliac crest. The length of both arms can be adjusted. This end goes into the peritoneal cavity, and this is introduced through the saphenous vein, up through the vena cava, to about the level of the diaphragm, or to the intrathoracic level.

(Slide) This shows a cross section and how it works. This is the chamber, and this flange on it has Dacron incorporated into it, so that it can be sutured to the periosteum. There are two valves that allow flow in only one direction, and they are both split valves of the same construction. The whole apparatus is made of silicone rubber. These are pressure-activated valves also. There is no critical opening pressure for either of these valves. They open with the slightest positive pressure, and they close with positive pressure on the distal end.

Compression of the chamber—and this is one of the essentials we believe—allows discharge of the fluid from within the chamber. It can be made of any size, but the ones we have been using are about 5 cc.

(Slide) This shows the manner in which all but two of these valves have been placed. In the two exceptions the chamber was placed over the pubis. I think this procedure does require general anesthesia, and in addition to what's shown here there has to be an incision below the groin to expose the saphenous vein. We haven't had any infection, and we have not had any clotting in eight patients.

Now, one of the differences between what Dr. LeVeen has reported and our experience is that six of our eight patients had ascites on the basis of extensive malignancy, and this particular patient had chylous ascites arising secondary to extensive reticulum cell sarcoma. She had been treated with radiation and extensive chemotherapy.

DR. L. R. EIDEMILLER (Portland, Oregon): This august body hardly needs to be reminded of the unsatisfactory nature of the medical therapy of ascites, consisting of fluid restriction, bed rest, diuretics, and thus further progression of catabolism, decreasing visceral perfusion, and the frequent precipitation of hepatorenal syndrome.

Side-to-side portacaval shunting for this problem carries a significant morbidity and mortality, with, frequently, further deterioration in hepatic function.

That relief of ascites may improve hepatorenal function has been shown by clinical observation, and documented by many writers. Retransfusion of ascitic fluid has been done on an intermittent basis, and shown to be of at least transient benefit. However, the general application of this principle has awaited the technical development of a suitable technique to make it logistically feasible over a long term.

We recently encountered an unusual case of Budd Chiari syndrome of undetermined etiology which demonstrated to us the effective use of the LeVeen peritoneal-venous shunt. A 34-year-old man was explored at another hospital for fatigue, weight loss and epigastric pain and jaundice. At laparotomy, he was found to have 200–300 cc of slightly bloody ascitic fluid, portal venous hypertension, and a swollen, turgid liver and spleen. No tumor could be identified. Liver biopsy showed canalicular biliary stasis and venous congestion, but no evidence of tumor.

Postoperatively, he did very poorly, and was transferred to our hospital with progressive ascites and hepatorenal failure. There an extensive workup failed to reveal the underlying cause of his illness, but vena cavography and attempted transjugular cholangiography revealed apparent thrombosis of the hepatic veins and the intrahepatic vena cava.

Visceral angiography confirmed the presence of portal hypertension, and also disclosed portal and splenic vein thrombosis. Again, no evidence of a tumor was seen.

By this time the patient was deteriorating rapidly, with massive ascites requiring daily paracentesis for increasing respiratory embarrassment. His hepatorenal failure and premoribund state made him a very poor candidate for any kind of surgery. However, the LeVeen shunt was placed under local anesthesia with a single injection of ketamine while the tunnel was made.

Certain modifications were required, because by this time he had also thrombosed his jugular venous system, and so we placed the venous end of the shunt through the cephalic vein, through our standard approach for axillary-femoral, or axillary-axillary bypass graft, and in so doing obviated the need to cross the clavicle.

(Slide) This displays the prompt recovery in hepatic and renal function after shunt placement, but it does not really demonstrate to you the dramatic clinical improvement which occurred in this patient. He was discharged at 14 days, ascites free, and now five months after operation has nearly normal liver function.

His underlying problem continues to defy diagnosis, but his clinical course has certainly been excellent.

Another instance where we feel that ascites plays a very critical role is the patient who has undergone portal systemic shunting, particularly in our current series at Oregon, of Warren distal splenorenal shunt. Many of these patients develop ascites in the postoperative period. I'd like to ask Dr. LeVeen, and also Dr. Warren, if they feel that the morbidity and mortality and perhaps slow recovery in some of these patients could be aided by placement of such a device.

Dr. Thomas C. Moore (Torrance, California): I'd like to comment upon the use of peritoneal-venous shunting and alternate means for the management of intractable ascites in early infancy.

Approximately ten years ago, in Muncie, Indiana, I managed a five-week-old infant with massive bile peritonitis, who had a spontaneous slough of the junction of the cystic duct, by means of a roux-Y anastomosis of the proximal jejunum to the small remnant of common hepatic duct.

The patient recovered, but developed massive and uncontrollable ascites four months following operation, associated with a roentgen demonstration of extrahepatic portal vein occlusion.

Dr. John Waldhausen, at the Indiana University Medical Center at the time, connected this infant's peritoneal cavity and the right atrium by means of a Holter valve. The ascites was relieved, and the patient did well during an approximate six months' period of followup, but was lost to followup when the family moved to Alabama shortly thereafter.

Due to a natural reluctance to plunge into medical publication, and not being sure quite what to call it, and feeling that no one would believe me anyway, this unusual experience has never been reported.

Recently at the Harbor General Hospital, Dr. Morris Asch, an associate, and I, had a patient with intractable chylous ascites—intractable to standard dietary means—that we were concerned about. Dr. Asch contacted Dr. LeVeen regarding the obtaining of one of his devices. However, in the interim we elected to employ hyperalimentation, and during a three-week period of hyperalimentation the chylous ascites disappeared and has not returned during a four-month followup.

Recent experiences with chronic peritoneal dialysis and implantable cannulas and chronic perivascular access conduits for hemodialysis and chronic parenteral ailmentation suggests the feasibility of the approach employed by Drs. LeVeen and Christoudias. Their method appears to be a safe and simple means of managing a difficult problem. It certainly is a major contribution.

Dr. Harry H. LeVeen (Closing discussion): In response to Dr. Waddell's comments, it is possible that other valves can be used, but they must be pressure activated. A slit valve is a flow-activated valve. Even the saphenous vein becomes incompetent at low pressures. One never knows whether those valve units employing a flushing pump thrombose and reestablish patency when a clot is flushed out of the tubing. Such a pump should not be necessary if thrombosis does not occur, and for that reason, one was not incorporated into our system. Such a device may be required and we can always add it; but, at this present moment, it doesn't seem necessary.

I want to thank Dr. Eidemiller for presenting his unusual case. Budd-Chari's syndrome carries such a grave mortality that it is remarkable that such a serious problem can be handled in such a simple manner and with such excellent results. I'd like to show you, if I may, some additional visual evidence of before and after therapy of some of these patients.

(Slide) This before and after picture shows a tense abdomen. The closeup shows how shiny his abdominal skin has become. He has edema of the lower half of his body as well due to the high abdominal fluid pressure. Postoperatively, his abdomen is flat and the edema is gone.

(Slide) This is another before and after picture of a man who lost 40 pounds of ascitic fluid after placement of the shunt.

(Slide) This man was sitting in another hospital awaiting attention for an ulcerating umbilical hernia, due to his tremendous ascites. They sent him to us and after a shunt we have repaired his hernia.

Most striking in all of these patients is the pinched facies with sunken cheeks and thin nose. Notice how the face fills out after this shunt has been done.

Estimation of the Functional Reserve of Human Liver

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Functional hepatic reserve was determined in 32 patients with known liver or biliary tract disease employing kinetic analysis of hepatic removal of indocyanine green (ICG). The initial removal rates of incremental doses of ICG (0.5, 1.0 and 5.0 mg/kg body weight) were plotted as a reciprocal against the inverse of dose (Lineweaver-Burk plot) to provide a means of determining maximal removal rate from submaximal doses (Rmax). This function equalled 3.40 mg/kg/min in ten patients with normal livers, but was only .24 mg/kg/min in eight patients with alcoholic cirrhosis. Portasystemic shunting did not further influence Rmax. Infiltrative liver disease had only a mild depressive effect on this function. The results show that hepatic function can be precisely quantitated by classical enzyme kinetics (Michaelis-Menten). If Rmax is an estimate of protein receptor mass for organic anions, then the technique may allow an indirect means for quantitating hepatocytes even in the presence of changes in blood flow or hepatic function. The profound depression in R_{max} observed in patients with alcoholic cirrhosis is consistent with the progressive loss in hepatic mass associated with this disease.

THE LIVER has a remarkable capacity to carry out a wide variety of synthetic, storage, excretory, and metabolic activities. In fact, approximately half of its mass can be excised with only transient changes in contemporary liver function tests.[1] An infinite capacity for regeneration further complicates quantitative assessment of hepatic functional reserve. For these reasons, advanced liver disease may avoid detection, and terminal phases of hepatic dysfunction are predicted with great uncertainty.

The excretion of organic anions such as bilirubin and bromsulfalein (BSP) have been useful indicators of liver disease. Analysis of BSP retention at a specified period of time (usually 45 minutes) following its administration into a peripheral vein, has been a most sensitive index of hepatocyte function. Local toxicity and tendency towards extrahepatic removal as liver disease progresses has detracted from its usefulness. Indocyanine green (ICG), a tricarbocyanine dye, has been employed with increasing frequency in its place since ICG is without reported toxicity and undergoes neither intrahepatic conjugation nor enterohepatic circulation, and is removed from the blood stream exclusively by the liver.[4,6,8,9] Furthermore, its presence in the blood can be accurately assessed even in the presence of hyperbilirubinemia.

Paumgartner and his colleagues[12] have demonstrated that removal of incremental doses of ICG obeys classical Michaelis-Menten kinetics. Kinetic analysis in rat and man confirmed the earlier work of Hunton *et al*[5] who demonstrated in dog that hepatic removal of ICG was a saturable process. Rikkers and I[14] have recently shown that maximal removal rate of ICG provides a quantitative estimate of hepatic mass, and that this estimate is valid for normal as well as regenerating rat liver. We further demonstrated that the technique could be used in the dog before and following 70% hepatectomy but not during the early and most rapid phase of regeneration.[13] The present communication relates the results of assessment of hepatic functional mass by ICG uptake in the normal and in patients with liver or biliary tract disease.

Materials and Methods

Thirty-two patients with known liver disease and ten patients without demonstrable hepatic dysfunction were

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selected for study. The latter were considered controls who represented the expected results from this test. Included in the group were three patients, one with chronic lymphocytic leukemia with normal liver biopsy, one with morbid obesity who had moderate fatty infiltration on liver biopsy, and a third with bleeding esophagitis with normal hepatic function. The remainder of the controls were volunteers from personnel working on the project. The abnormal group consisted of eight patients with alcoholic cirrhosis studied pre-shunt, five patients with biliary or post-necrotic cirrhosis studied pre-shunt, five patients studied at various intervals following portal decompression, and 14 patients with a variety of pathological disturbances of the liver or biliary tree. Eight patients were studied before, and one or more times following, portacaval shunt (five had two post-shunt studies). Fourteen patients underwent 18 studies at an interval of one week to sixty months following portal decompression.

Protocol For Measurement of Maximal ICG Uptake

Indocyanine green (Hynson, Westcott and Dunning, Baltimore, Maryland) was dissolved in 20 ml of distilled water and 5 ml of 5% human albumin to provide a 2 mg/ml solution prepared fresh each day. Fasting subjects were provided doses of 0.5, 1.0, or 5.0 mg/kg body weight on alternate days by an intravenous route. Blood was withdrawn before and at 5, 10, and 15 minute intervals following ICG administration. Upjohn heparin which contains benzyl alcohol as a preservative, was used to wet the surface of syringes to prevent clotting. Following centrifugation, serum was analyzed for ICG by determination of its optical density in a Spectronic 70 spectrophotometer (Bausch and Lomb, Rochester, New York) at 800 μ. Concentration was determined by comparison to appropriate standards. Plasma disappearance rate of ICG was ascertained by regression analysis of the natural logarithm of optical density or ICG concentration of recovered samples as a function of time. Multiplying the plasma disappearance rate (PDR) which is equal to slope of regression times dose yields initial removal rate of dye (R). Maximal removal rate (Rmax) was calculated by regression analysis of the reciprocal of initial removal rate (R) against the reciprocal of dose (D).

Kinetics of ICG Removal

The conceptual basis for the present analysis of hepatic function rests on an analogy to classical enzyme kinetics as described by Michaelis and Menten.[11] In the analogy, ICG (substrate) interacts with a theoretical hepatic receptor (enzyme) on the sinuoidal side of the hepatocyte. Removal of ICG from the blood by this mechanism is depicted by the following equation:

$$(\mathrm{ICG}) + (\mathrm{H}) \underset{k_2}{\overset{k_1}{\rightleftharpoons}} (\mathrm{ICG} - \mathrm{H}) \xrightarrow{k_3} (\mathrm{ICG}') + (\mathrm{H})$$

where,
(ICG) = ICG dose
(H) = hepatic receptor
(ICG-H) = ICG-receptor complex
(ICG′) = ICG released from the receptor into the hepatocyte k_1, k_2, and k_3 = association and dissociatio constants of the complex

When hepatic removal rate of ICG is proportional t concentration of its complex with hepatocyte receptors instantaneous removal rate is described by the followin equation (Michaelis-Menten):

$$R = \frac{\mathrm{Rmax} \times (\mathrm{ICG})}{\mathrm{Km} + (\mathrm{ICG})}$$

where,
R = PDR × dose = initial removal rate in mg per k per min of an individual ICG dose Rmax = initial maximal removal rate in mg per kg per min or the rate o hepatic ICG uptake when all receptors are complexe with ICG

$$\mathrm{Km} = \frac{k_2 + k_3}{k_1} = \text{Michaelis constant}$$

Figure 1 (top) is a schematic representation of th Michaelis-Menten equation which results in a rectangular hyperbola with R asymptotically approaching Rma at high doses. Km represents the affinity of hepatic receptors for ICG and is equal to the dose which provide for half-maximal removal rate. Linear transformation o the Michaelis plot by the method of Lineweaver-Burk as shown in Fig. 1 (bottom), provides a convenient wa to calculate Rmax from submaximal doses of dye.[10] Thi is fortunate since receptor-ICG interaction may be mor accurate at lower doses if indeed the analogy to substrate enzyme interaction is correct. In practice, linearit of the Lineweaver-Burk plots were determined by regression analyses and Rmax was calculated from the intercept by division to unity. Barber analysis[2] was employed to compare Rmax's and Km's of controls and alcoholic cirrhosis. Grouped data was also subjected t unpaired t analysis. Liver function tests were obtaine by multi-channel analyzer in the clinical laboratories o the respective institutions where patients were studied

Results

The characteristics of the plasma disappearance o ICG over a fifteen-minute interval is shown in Fig. 2 fo a control and a patient with alcoholic cirrhosis. In eac instance the plasma disappearance curve is linear. Th

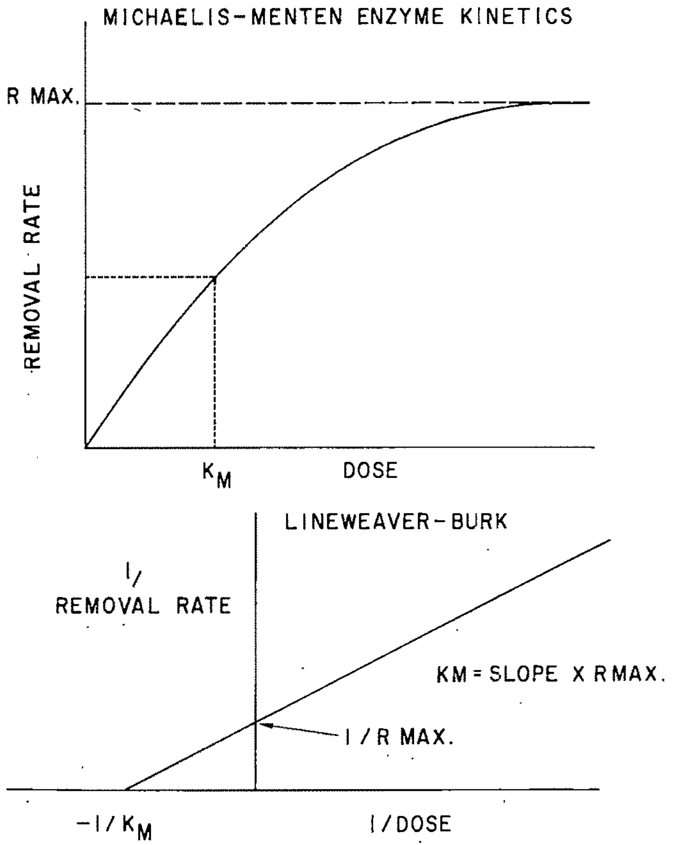

FIG. 1. (Top) Schematic representation of a Michaelis plot. Initial removal rate is plotted as a function of dose. As dose increases, removal rate reaches an asymptote which represents maximal removal rate (Rmax). (Bottom) The Michaelis plot has been transformed to a straight line by relating the reciprocal of removal rate to reciprocal of dose. The Y intercept represents reciprocal of (Rmax. Km can be calculated by multiplying slope times Rmax.

slower removal rate (shallower slope) seen in the alcoholic cirrhotic was characteristic of this group.

Maximal removal rate of ICG was ascertained 63 times in 42 individuals thereby providing 189 plasma disappearance curves. Nearly two-thirds (62%) of PDR's demonstrated a correlation coefficient equal to or greater than .997, the value which provides a p value of less than .05 for 3 points. Eighty-six per cent provided a correlation greater than .98. In five instances, only two of the three plasma concentrations were used to obtain a PDR since best fit calculations revealed an obvious analytical discrepancy in the values obtained with the three-point analysis.

Forty-four Lineweaver-Burk regressions demonstrated correlation coefficients equal to or greater than .997 ($p < .05$). Eighty-one per cent were greater than .98. Inspection of those values which fell below .98 did not reveal a consistent source for error. In two instances, PDR's with low correlation may have contributed to discrepant results. In most cases, however, poor correlations on the Lineweaver-Burk plot did not relate to erratic PDR's, but rather appeared to be a reflection of a true change in hepatic function. For example, a patient recovering from halothane jaundice (A.M., 53-year-old female, Table 1) gave an Rmax of .41 with an R of .96, but all PDR correlations were above .998. Controls gave relatively uniform values, with six of ten having correlations greater than .997. In one of four in which the correlation was less than .997, an extension to five-dose analysis to yield a highly significant correlation only provided a minor change in Rmax (an increase from 1.0 to 1.7 mg/kg/min). Failing to find a consistent way to exclude Rmax's with a regression coefficient less than .997, all values obtained were used in the following analyses.

Figure 3 compares a Michaelis plot of controls to that of alcoholic cirrhotics before portal decompression. The Rmax's represented by the horzontal dashed lines were calculated by regression analysis of the reciprocal of removal rate and dose. The points inscribe the actual values observed and the solid line represents the Michaelis plot calculated from the Michaelis-Menten equation. Vertical broken lines identify the respective Km's. It can readily be appreciated that the observed removal rates for controls is well below the maximal removal rate calculated from the observed values. In fact, the 5 mg/kg dose is significantly less than that required to

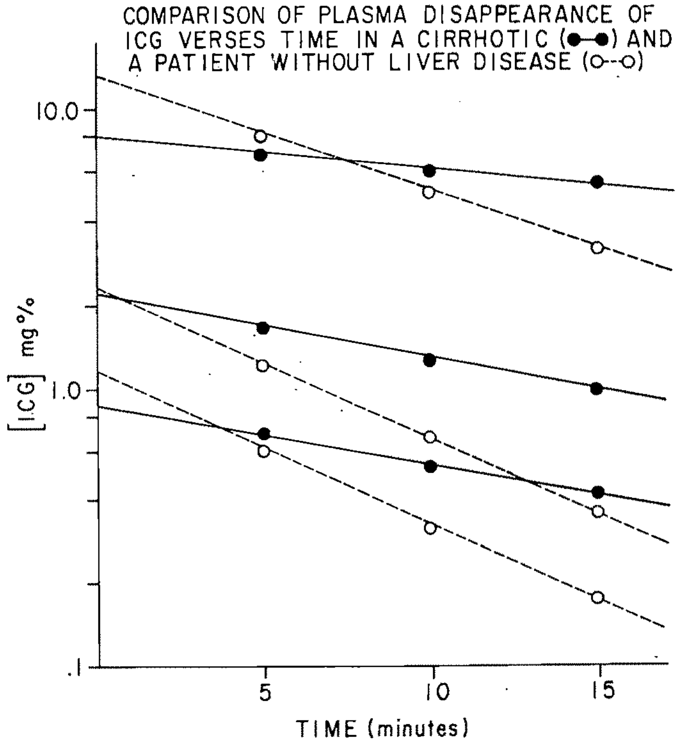

FIG. 2. This represents a semilogarithmic plot of serum concentration of ICG as a function of time. The broken line represents the plasma disappearance curve for a normal subject; the solid line represents this function for an alcoholic cirrhotic.

TABLE 1. *Clinical Correlation Between Rmax and Hepatic Function in Patients With Liver or Biliary Tract Disease*

Patient	Age/Sex	R_{max}	r	Total Bilirubin	Alk. Phos.	Albumin	Diagnosis
F. M.	62 F	3.36	.998	0.5	78	3.2	Methotrexate fibrosis
E. M.	50 F	1.84	1.000	2.0	474		Bile duct stricture, pericholangitis
A. M.	53 M	1.20	1.000	0.6	133	3.0	Caroli's disease with hepatic stones
E. D.	36 F	1.56	.998	1.1	55	3.9	Early cirrhosis, fatty infiltration
H. M.	41 M	1.61	.995	10.0	340	3.2	Sclerosing cholangitis, post colectomy ulcerative colit
D. W.	51 M	1.08	.979	0.6	50	4.1	Massive hemangioma
S. R.	28 M	.91	.985	0.9	58	4.8	Acute cholecystitis, post-op
R. D.	61 F	.88	1.000	1.7	199	2.6	Metastatic liver carcinoma, extensive
S. T.	30 F	.87	.996	1.5	228	4.1	Pericholangitis, post colectomy ulcerative colitis
J. B.	52 M	.78	1.000	1.6	98	2.8	Sarcoidosis with liver involvement
H. L.	30 M	.42	.999	1.2	93	3.5	Renal transplant—one year
A. M.	57 F	.47	.960	15.0	560	1.8	Halothane hepatitis
R. C.	40 M	.34	.981	8.6	320	3.0	Alcoholic hepatitis, bile duct stricture
F. F.	40 M	.18	.924	6.3	720	3.3	Pericholangitis, post colectomy ulcerative colitis

give a half-maximal response. On the contrary, a 5 mg/kg dose in the alcoholic cirrhotic group elicits a near maximal response. The Lineweaver-Burk plot for these data are shown in Fig. 4. Regression lines are distinctively different as are the respective reciprocals of Rmax. The Y intercept yields an Rmax of 2.11 mg/kg/min for controls and .19 mg/kg/min for cirrhotics. Because of the sizable variance in the removal rates of the cirrhotic population, it was necessary to calculate confidence limits by regression analysis as described by Barber. This analytical method provided an Rmax of 3.40 mg/kg/min with 95% confidence limits of 3.11 to 3.72 for controls. The cirrhotic group gave an Rmax o .24 mg/kg/min with limits of .18 to .31. As can be seen there was no overlap between groups providing a hig level of statistical significance. The Km's were also derived by Barber analysis yielding a value of 8.22 an 4.14 respectively for controls and alcoholic cirrhotic without overlap in their 95% confidence limits. This re

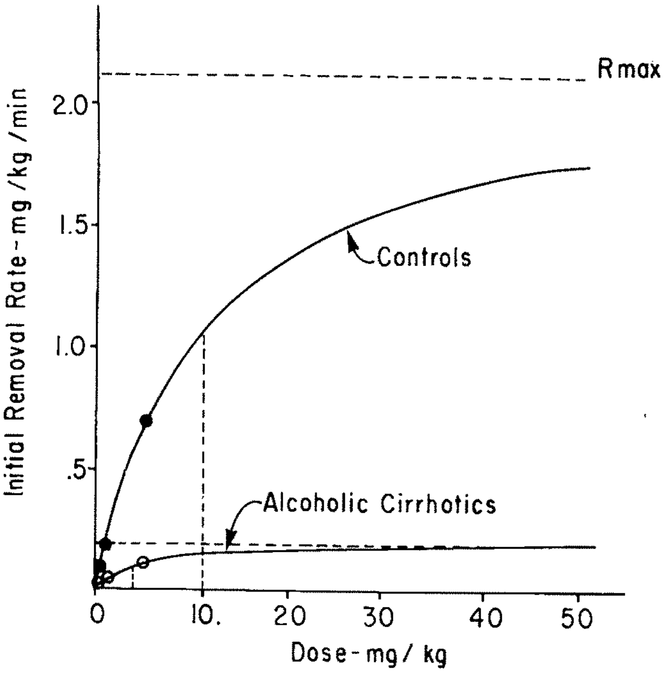

FIG. 3. The upper line represents the Michaelis plot for 10 controls, as compared to that obtained for eight alcoholic cirrhotics (lower line). The horizontal dashed lines represent Rmax's calculated from the Lineweaver-Burk regression obtained from the data points for removal rates at the three doses studied. The vertical dashed lines identify the respective Km's.

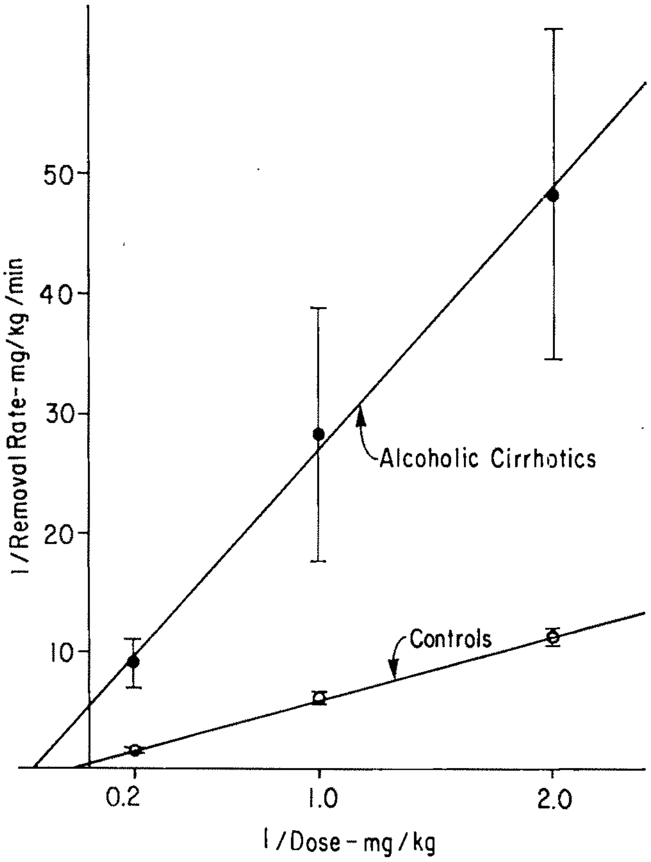

FIG. 4. These Lineweaver-Burk plots for controls and alcoholi cirrhotics demonstrate a high degree of linearity for grouped dat (r = .9999 and .9985 respectively for controls and cirrhotics) The points represent the means bracketed by their standard error

TABLE 2. *Clinical Correlation: Alcoholic Cirrhotic Group*

Patient	Age/Sex	R_{max}	r	Bilirubin	Alk. Phos.	Trans.	Alb.	P. T.	BSP
L. J.	40 M	.49	.999	.8	60	27	2.6	85%	2%
A. M.	50 F	.27	1.000	1.0	102	25	3.1	92%	
M. P.	35 F	.25	.995	.7	128	149	3.0	52%	29%
M. H.	48 F	.25	.992	1.0	46	136	3.9	100%	3%
C. H.	43 M	.21	1.000	1.2	115	75	4.3	90%	
D. B.	51 M	.12	.970	1.1	110	60	3.3	65%	
H. E.	44 M	.06	.996	3.2	107			38%	24%
T. O.	58 M	.07	.986	7.6	110	75	2.0	63%	

sult suggests that the hepatocytes of the alcoholic cirrhotic have a decreased affinity for ICG uptake, although interpretation of the true meaning of Km in this context requires further study. Inspection of the Km's for various other groups did not reveal any consistent relationships which might provide a further clue as to the meaning of this particular function.

A comparison of maximal removal rate to conventional hepatic function indices (total bilirubin, alkaline phosphatase, and serum albumin) for a variety of diseases of the liver and the biliary tree, are shown in Table 1. Inflammatory lesions of the bile duct did not appear to significantly affect Rmax except in one case (F.F.) where an extremely poor correlation was obtained for the Lineweaver-Burk transformation. Likewise, infiltrating diseases were accompanied by only a moderate depression of Rmax.

Comparative liver function studies for alcoholic cirrhotics are shown in Table 2. The random nature of changes in traditional liver function tests is well demonstrated in this group. For example, two patients had normal BSP retention (L.J. and M.H.) with only a single disturbance in other parameters measured. Two additional patients (A.M. and C.H.) had only minor changes in hepatic function, but profound depression in maximal removal rate of ICG. It is apparent that the two patients with the lowest Rmax's (H.E. and T.O.) also had the most marked changes in the usual parameters used to assess hepatic function. All eight patients had gross and microscopic evidence of advanced cirrhosis. Figure 5 compares the Rmax of patients with alcoholic and non-alcoholic liver disease. Two of the controls presented in Figs. 3, 4 have been omitted since their Y intercepts (1/Rmax) gave Rmax values (18.52 and 344.8) which appeared spuriously high as a consequence of the closeness of the intercept to the origin.

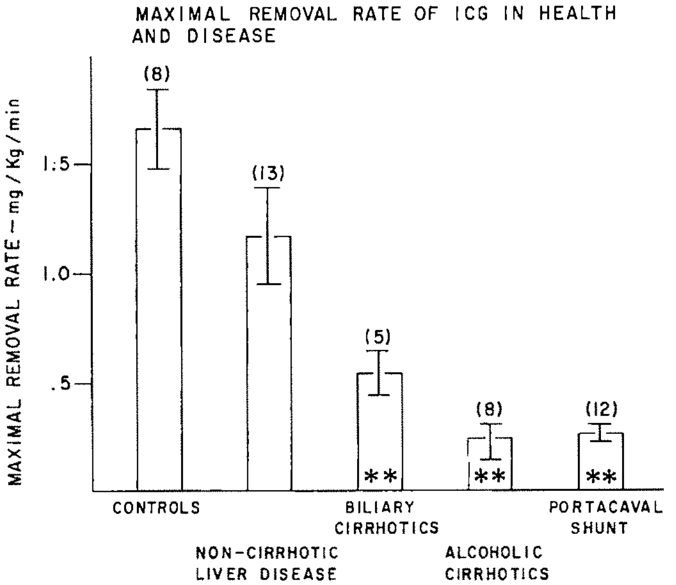

FIG. 5. This histogram represents the mean plus or minus the standard error of Rmax's for controls and for a variety of diseases of the liver and biliary tree. Numbers in parentheses represent the population size.

Figure 5 compares the Rmax of patients with alcoholic and non-alcoholic liver disease. As can be seen, non-cirrhotic liver disease as a group, did not differ from controls. Cirrhotics, however, before and after shunting, demonstrated a highly significant decrease from normal. The effects of portacaval shunting was studied in a systematic manner in eight patients, five with alcoholic cirrhosis and three with biliary or post-necrotic cirrhosis. In the alcoholic group, three patients were studied one week and at three months following portal decompression; one additional patient was studied early (one week) and another at 2½ years. In the biliary or post-necrotic group two patients were studied at one week and again at three months and a third patient was studied three months following surgery. No significant difference was found between Rmax before or at intervals after shunting in either of these groups, confirming the impression that portal decompression did not influence this aspect of hepatic function.

An attempt was made to relate bilirubin, alkaline phosphatase, transaminase, albumin and prothrombin time to levels of Rmax. The only significant correlation occurred between bilirubin and Rmax of the post-portal decompression group. In this case, there was a negative correlation of .5656 ($p < .05$) thereby revealing an inverse relationship between bilirubin and Rmax. This was not true, however, for other groups, although correlations for alcoholic cirrhotics were close to a level of significance with a negative correlation of .6020 ($p < .1$ but $>$ than .05). Regression analysis also revealed a highly significant correlation between PDR's at all doses and respective Rmax's, with the 5 mg/kg dose giving the highest correlation coefficient (.822, $p < .01$). This is consistent with the observation that this dose approached a near maximal level in the alcoholic cirrhotics, the population which showed the largest depression in maximal removal rate.

Discussion

Results of the present study confirm that hepatic uptake of incremental doses of ICG in human is a saturable process which can be subjected to analysis utilizing the concepts of classical enzyme kinetics. In this analogy, ICG participates as a substrate, and the hepatic receptor mechanism functions as an enzyme. The linearity of the plasma disappearance rate of individual doses of ICG in both the normal and in patients with liver disease reflects first order kinetics and allows use of Michaelis-Menten analysis and its linear transformation by Lineweaver-Burk plot. We were surprised to find such a reasonable correlation for the linear regression of the reciprocal of removal rate versus dose with only three-point analysis. Linearization of this function by Scatchard plot[15] did not appreciably change the result. Possibly four or five-point analysis would have greatly increased the confidence level of individual maximal removal rates, but expense and inconvenience to the patient precluded such an approach in this initial survey.

The Rmax obtained from controls by Barber[2] analysis of grouped data gave a value which was comparable to that observed by Paumgartner[12] and his colleagues (ca 3.5 mg/kg/min). Their alcoholic cirrhotics, however, provided an Rmax in the range of .7 mg/kg/min, a value about three-fold greater than that seen in the alcoholic cirrhotics in the present study where Rmax equalled .24 mg/kg/min with confidence limits of .18 to .31. Since comparable techniques were employed, it is likely that the latter group were more advanced in their alcoholic liver disease.

We had hoped that this test would provide a way to quantitate hepatic functional reserve of cirrhotics who were to undergo portal decompression for esophageal varices. One individual (T.O.) with a low Rmax died in the early postoperative period from progressive hepatic and renal failure, but a second (H.E.) with an equally low value has now survived for two and one half years with an Rmax that remains at a very low level (.15 mg/kg/min). The data suggest that portacaval shunting has no influence on maximal removal rate of dye. Sufficient numbers of patients have not been studied for a long enough period of time to conclude that major portal diversion does not lead to progressive loss of hepatic mass. Acute changes in hepatic blood flow which may accompany a shunt, however, do not appear to interfere with this particular function. We have found this to also be the case following performance of end to side portacaval shunt in the rat (unpublished results).

There is controversy as to whether single dose analysis of ICG is a more useful or sensitive test than BSP for identifying liver disease.[3] Comparison of Rmax with plasma disappearance rates of individual doses of ICG in the present study did establish a high level of correlation with all doses, but especially the largest (5 mg/kg). A single large dose may be an accurate way to follow progression or resolution of liver disease if the dose is near maximal such as was seen for the 5 mg/kg dose in the alcoholic cirrhotic. A 10 mg/kg dose may even have provided a better index of maximal removal rate. We found this to be the case during the rapid phase of regeneration following two-thirds hepatectomy in the dog.[13] This dose, however, was accompanied by emesis in these studies. Furthermore, high doses are known to cause cholestasis in experimental animals.[7] If this is also true for the human, then retention of bilirubin and bile salts could be accentuated by such a test. We did not observe an adverse effect on serum bilirubin levels at doses employed in the present study.

A statement as to false positives and false negatives cannot be made with such a small number of studies. In fact, the measurement of Rmax is viewed by us as a potential tool for attempting to quantitate hepatic function and not as a practical clinical means for the differential diagnosis of liver disease. Refinement and perfection of this approach, however, may provide a means for identification of occult liver disease or end-stage hepatic dysfunction. The development of a quantitative prognostic index for acute or chronic liver disease will require larger clinical experience that relates Rmax to ultimate outcome.

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DISCUSSION

DR. ROBERT ZEPPA (Miami): I have just a few questions. Is it possible that the test is just too sensitive for the information that we seek concerning individuals with cirrhosis?

For example, if the protein receptor mass, whether this is in that group of protein receptors that have been labeled X and Y proteins, if this protein mass is not synthesized at the same rate as other proteins, as, for example, albumin, fibrinogen, prothombin, then perhaps it will indicate a very severe problem, as he has suggested with his data, but may not be functionally relevant to prognosis for the patient.

Taking it the other way, in a regenerating liver where normal cellular function appears to be returning, because the cells themselves are normal, one can utilize the technique to correlate well with the regenerating mass. In a liver that has hepatocellular dysfunction, if the dysfunction is spotty in terms of all of the functions of a liver cell, it may be possible, or even likely that this technique may be just too sensitive.

DR. HARRY H. LEVEEN (Brooklyn): We are interested in whether absorbed ammonia might be toxic to the liver cell and impedes its regeneration. I would greatly like to hear Dr. Moody's comments as to whether his model might be applied to studying the effect of diet, drugs, poisons and ammonia on liver regeneration.

DR. FRANK G. MOODY (Closing discussion): We're just beginning to study hepatic reserve in surgical patients. Paumgartner and his colleagues have explored this technique in medical patients, and we have tried to carry it a bit further, relating it to hepatic mass, protein receptors, and possibly the function of Y and Z proteins. The manner whereby organic anions gain entrance into the hepatocyte is unknown. We have hopes that R max is a measurement of the number of hepatocytes present, as well as an indicator of a disturbance in organic anion transport.

In answer to Dr. Zeppa's question, I would look at it in quite the reverse, that probably this is a more stable function than looking, for example, at something that has to be metabolized in the hepatocyte, or has to be secreted by the cannuliculus. We assume that we are looking at a function on the sinusoidal side of the hepatocyte and, therefore, are observing membrane function of the transport process to get these organic anions into the cell.

In answer to Dr. LeVeen, we haven't tried to hold back regeneration. We have learned several things about this particular function, however. One is that if you do an acute portacaval shunt in the rat, it does not influence this particular parameter. Although at low doses blood flow influences the PDR, in high doses the PDR is primarily a reflection of hepatocellular function. If you use the whole dose range, then you eliminate these variables, which is an important consideration, because the ICG just has to get there; it doesn't make any difference how long it takes it to get there (within reason) or how it gets there. I think that's the value of the test.

We have done only one other study, and that's trying to enhance regeneration, initially in normal rat liver, and now with regenerating rat liver. Our next approach is to see if we can enhance regeneration possibly with some of the nonspecific mitogens, but we haven't done anything to try to hold back regeneration, and I think it might be an interesting model to try it in.

Alpha Fetoproteir

An Index of Progression or Regression of Hepatoma, and Target for Immunotherap

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Clinical and laboratory studies of AFP producing hepatomas demonstrated that: 1) serum AFP levels correlated directly with tumor growth; 2) circulating AFP could be cleared by passive administration of an excess of anti-AFP; and 3) highly specific anti-AFP functioned as a carrier to localize diagnostic and possibly therapeutic amounts of radioactivity in hepatoma tissue. These studies helped elucidate certain criteria which should be fulfilled before attempts to initiate passive humoral immunotherapy of cancer are undertaken.

ALPHA-FETO PROTEIN (AFP) is an albumin-like plasma protein present in low concentrations in the sera of normal adults and frequently found in abnormal amounts in the sera of patients with hepatoma and teratocarcinoma, and occasionally in other varied malignancies.[1] Fluorescent antibody techniques have demonstrated increased cytoplasmic, membrane, and perinuclear concentrations of AFP in malignancies producing this protein,[10] and Day[3] suggested that antigen so localized might be used to concentrate antibody carried antitumor activity to AFP producing cancer cells. However, studies evaluating the anti-tumor activity of anti-AFP alone or as a carrier of isotopic or chemotherapeutic agents have with a single exception[8] failed to demonstrate a significant tumoricidal effect.

A review of those studies suggested that certain principles broadly applicable to humorally mediated i munotherapy may not always have been adhered including: 1) the use of antisera of high affinity, sp cificity, and concentration; 2) clearance of circulati tumor antigen prior to administering antibody intend to localize on tumor tissue; 3) application to a st of minimal disease; and 4) maintenance of antibo excess for significant periods. However, AFP-produci malignancies possess uniquely advantageous features f evaluation of antibody therapy including: 1) the cility with which excellent antisera can be produce 2) the availability of simple, rapid methods for monit ing circulating tumor associated antigen; 3) a typica irreversibly fatal disease course; and 4) the presen of an excellent animal model of the human disease, t BW 7756/C57L murine hepatoma. Thus, we underto the following studies of techniques for humoral immun therapy in the belief that the findings might be use not only in the control of AFP producing malignanci but might also prove generally applicable.

Materials and Methods

Human Studies

Patient sera were tested for AFP using as antisera rabbit antihuman AFP* produced against human te fetal cord blood and absorbed with normal hum plasma. The antisera activity was adjusted to produ a positive reaction against sera containing AFP 5

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* Ortho Diagnostics, Division of Ortho Pharmaceutical.

* Ortho Research Foundation, No. 10467 Lot 105.

ngm/ml when reacted for one hour by counterimmunoelectrophoresis (CEP) and examined under optimal precipitin recognition illumination.* Patient AFP sera levels are reported as the highest titer producing a definite reaction under these conditions.

Patients with hepatoma were given palliative chemotherapy with systemic 5-FU, 12 mgm/kg IV q week, except for the two cases whose course is illustrated in detail. All diagnoses of malignant or benign disease were established by histopathologic study.

Animal Studies

Preparation of Antisera. Rabbit anti-murine AFP was produced by immunizing 2 kg New Zealand rabbits with 16–17 day C57L/J fetus according to the method of Kahan and Levine.[6] Whole rabbit sera was absorbed with normal adult C57L/J sera and liver powder until judged monospecific by gel diffusion. An IgG fraction was prepared from the absorbed sera by DEAE cellulose† column chromatography and its specificity and anti-AFP activity tested by immunoelectrophoresis and gel diffusion. This preparation is hereafter termed "anti-AFP$_1$". Further purification of anti-AFP was obtained by precipitation of antigen-antibody complexes, centrifugation, washing of the precipitate, low pH complex dissociation and Sephadex G-150‡ column separation according to the method of Nishi.[9] This preparation is hereafter termed "anti-AFP$_2$". Normal rabbit and immune IgG were radioiodinated with ^{131}I by the chloramine-T method as described by McConahey and Dixon.[7] The radiolabeled protein was separated from free iodine by filtration over Bio-gel P-60. The specific activity obtained ranged from 0.3 to 0.6 u Cu per ugm protein. The immune and normal sera used in each experiment were adjusted to contain equal amounts of protein and specific activity.

Tumors were transplanted by skin incision and subcutaneous placement of 0.02 to 0.05 gm pieces of fresh tumor tissue. Established tumors were termed "small" in size if they weighed 0.10–0.25 g; of "moderate" size if weighing 0.26–0.99 g; and "large" if weighing more than 1.0 g. All antisera were administered by intraperitoneal injection.

Testing of Antisera. The prepared antisera were reacted by gel diffusion against sera from normal and hepatoma bearing adult C57L/J mice, amnionic fluid, and tissue extracts of C57L/J fetuses and adult mice. A standard antiserum and positive control were selected for use as baseline references throughout these studies, and stored in aliquots at –70 C. Murine sera were titered for AFP using the CEP technique previously described. Fluorescent localization of AFP was performed on frozen sections using a two-step bridge consisting of rabbit anti-AFP and fluorescein conjugated goat antirabbit gamma globulin.*

Clearing of AFP; Effect of Anti-AFP$_1$, on Tumor Growth. (Group 1) Animals with moderate sized hepatomas were given a single injection of 0.5 ml of anti-AFP$_1$, and their AFP levels titered at 1, 12, 24 and 48 hours. Control animals received injections of PBS or non-immune IgG and their AFP titers were also measured at 1, 12, 14 and 48 hours.

(Group 2) Animals were given daily doses of 0.25 ml or 0.50 ml of either anti-AFP$_1$ or non-immune sera, or 0.50 ml of PBS for 14 consecutive days after implantation of 0.02–0.05 g of tumor and their AFP levels studied at approximately two-day intervals thereafter. All animals were sacrificed at day 14 and each tumor weighed to detect any effect of anti-AFP$_1$ on tumor growth. Histologic sections of these tumors were prepared to help evaluate any anti-tumor effect.

Localization of ^{131}I Labeled Anti-AFP$_1$ and Anti-AFP$_2$ in Tumor Tissue. (Group 3) Animals four days post transplant of .02–.05 g tumors were cleared of circulating AFP by injection of 0.5 ml whole anti-AFP sera, and 24 hours later given 8 u Cu of ^{131}I labeled anti-AFP$_1$ or non-immune rabbit IgG. Control and treated animals were sacrificed daily thereafter and the specific activity of tumor and normal tissues determined by measurement in a deep well scintillation counter. The percentage of injected dose found per gram of tissue, and a tumor:blood ratio of specific activity were calculated with the following formulas:

$$\% \text{ Dose/g} = \left(\frac{\text{Counts/g Tissue}}{\text{Counts administered}}\right) \times 100\%$$

$$\text{Tumor: Blood Ratio} = \left(\frac{\text{Counts/g Tissue}}{\text{Counts/g Blood}}\right) \times 100\%$$

(Group 4) Animals four days post transplant of 0.02 g or ten days post transplant of 0.05 g of hepatoma tissue were cleared of circulating AFP and given one u Cu amounts of ^{131}I labeled anti-AFP$_2$ or control IgG. One set of animals receiving the anti-AFP$_2$ was not initially cleared of circulating AFP. The counting and calculation of isotope localization was performed as for Group 3 animals.

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* Hapindex Systems, Ortho Diagnostics.

† Whatman DE-52.

‡ Pharmacia.

* Cappel Laboratories.

TABLE 1. *AFP Titers in Liver Disease*

Condition	No. Pos/Total	Titer Range	Observations
Hepatocellular Carcinoma	16/25 (76%)	1:1 to 1:2560	Typically q monthly
Metastatic GI Carcinoma Gastric 2; Pancreas 7; Colon 16	0/25		2, one month apart
Resection for Benign Disease Adenoma 2; Trauma 1	0/3		Daily × 10, and at 1 mon
Acute Hepatitis Halothane 1; HAA pos. 4; ? Drug 1	0/6		2, one month apart
Extensive Intrahepatic Abscess	0/1		2, one month apart

Results

Human Studies

Alpha-fetoprotein activity in various types of benign and malignant disease is shown in Table 1. The AFP titers of hepatoma patients varied greatly and there was no correlation between patients as to the amount of clinical disease present and the serum AFP level observed. However, when each patient was used as his own control the AFP titer and the clinical status correlated well. No relationship between histology and AFP production was found, and in particular, the AFP negative hepatomas were not morphologically distinctive. Serum AFP titers were frequently observed to decrease in the terminal stages of disease, but a cause for this was not identified. Three AFP positive hepatoma patients were also HAA positive. Each had received many blood tarnsfusions and the sequence of the antigenemias could not be established.

Patients recovering from hepatic resection for benign disease or from acute drug or viral mediated hepatic injury were never observed to have elevated serum AFP levels although AFP production has been reported to accompany some instances of hepatic regeneration in animals[1] and man.[12] The significance of this findi is that continued elevation of AFP levels in patien post hepatic resection for tumor appears more like to reflect residual malignant disease than regenerati hepatic processes. In this regard it is also worth em phasizing that the patient with extensive intra-hepat abscess formation did not have elevated AFP level Continued AFP positivity occurred only in patien with persistent malignancy.

Two patients had hepatomas resected for cure. each instance abnormal serum AFP levels returned normal over a period of time consistent with a six-d half-life for circulating AFP.[5] Recurrent disease was fi detected by reappearance of elevated AFP levels a could not be identified by conventional scans (includi gallium) or arteriograms until 2–3 months later. Inte sive palliative therapy produced significant decreas in AFP titers and concomitant clinical improveme (Fig. 1). One patient underwent selective venous sa pling which failed to identify the site of recurrence though the venous drainage from that site was ul mately shown to be among those sampled (Fig. 2

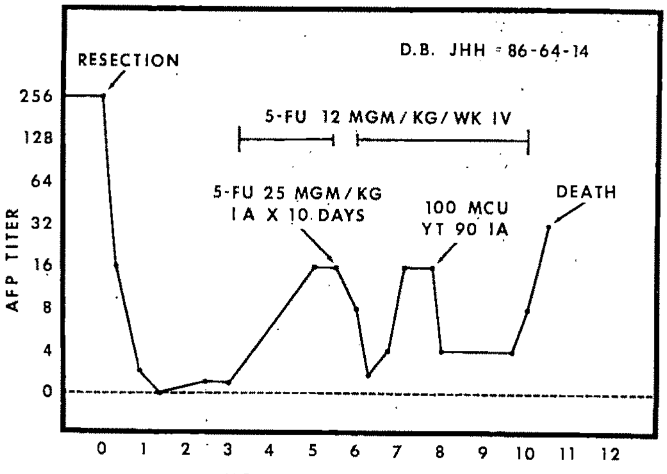

FIG. 1. Correlation of AFP titer and clinical course in a patient receiving intensive palliative therapy for recurrent hepatoma.

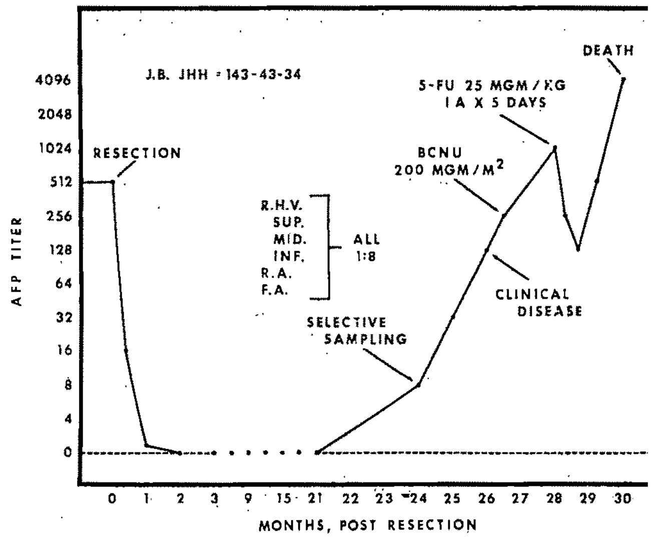

FIG. 2. Diagnosis of preclinical recurrent hepatoma by AFP stud but failure to detect tumor site by selective venous sampling localized AFP elevation.

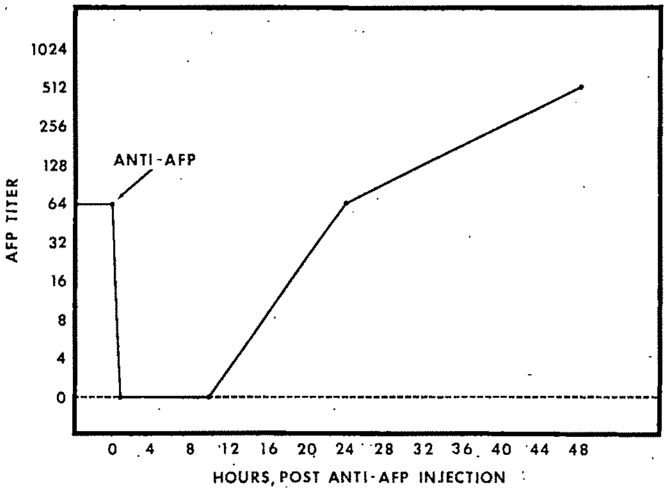

FIG. 3. Effect of a single injection of 0.5 ml of whole sera anti-AFP on the AFP titers of mice with 0.5 to 1.0 g hepatomas.

Effective palliative anti-tumor therapy did not cause any transient elevation of serum AFP levels which might be expected to accompany tumor cell destruction.

Animal Studies

Nature of Antisera. The antibody used reacted with identity by gel diffusion against fetal extracts and sera from hepatoma bearing mice, but not with sera from adult normal mice. Fluorescent antibody studies utilizing this antisera showed specific reactivity against the cytoplasm, membranes of hepatoma cells, and intercellular fluid of hepatoma tissue. Serum levels of AFP of hepatoma bearing animals could be titered by CEP and correlated directly with the growth of the tumors.

Clearing of AFP and the Effect of Anti-AFP$_1$ on Tumor Growth. The sera of hepatoma bearing animals, positive for AFP at a titer of 1:64, could be "cleared" of circulating AFP by injection of 0.5 ml of anti-AFP$_1$, which caused AFP titers to fall to zero within one hour of injection. This effect was short-lived as AFP activity was again present in blood taken 10–18 hours post-injection (Fig. 3). Animals receiving repeated injections of 0.25 or 0.5 ml of anti-AFP$_1$ for 14 consecutive days after tumor inoculation remained clear until day eight when their AFP levels began to increase rapidly. This "breakthrough" occurred at an identical time and rate for both the animals receiving 0.25 and those receiving 0.50 ml of anti-AFP$_1$ (Fig. 4). Control animals receiving PBS or 0.25 ml of non-immune IgG showed a rapid, progressive elevation of their AFP titer from day one until sacrifice.

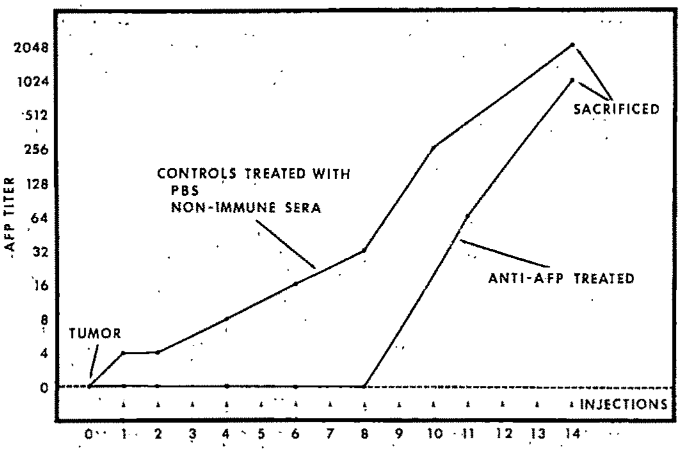

FIG. 4. Effects of injections of whole sera anti-AFP and non-immune sera on the AFP titers of mice with 0.1 to 0.5 g hepatomas.

The weights of the tumors taken on day 14 from animals treated with multiple anti-AFP$_1$ or control injections did not differ significantly and are shown in Table 2. Histologic sections of these tumors did not show any difference in degree of necrosis, fibrosis, encapsulation or inflammatory response. The fact that animal weights did not vary significantly suggests that such antigen-antibody complex disease as occurred was not deleterious within the short interval of this study.

Localization of ^{131}I labeled Anti-AFP$_1$ and Anti-AFP$_2$ in Tumor Tissue. ^{131}I radiolabeled anti-AFP$_1$ administered to animals with moderate sized hepatomas who were cleared of circulating AFP failed to localize specifically in hepatoma tissue. Tumor activity was higher than that of any other tissue but similar for animals receiving immune or non-immune sera (Table 3). This distribution of activity showed no significant change with time. The activity of blood remained surprisingly high and contributed much of the nonspecific activity observed for these vascular tumors.

Similar high but nonspecific tumor activity was also found in localization studies of anti-CEA and thought to reflect accretion of inert labeled IgG.[11] Studies to determine the effect of increasing the ratio of anti-AFP:nonspecific protein in the antisera were conducted with ^{131}I labeled anti-AFP$_2$ in animals with small hepatomas who were cleared of circulating AFP. Under these conditions anti-AFP$_2$ specifically localized in tumor tis-

TABLE 2. *Tumor and Animal Weight After 14 Consecutive Days of Treatment With Anti-AFP or Control Preparations*

Group	Treatment	Animal Weight Grams ± 1 SD	Tumor Weight Grams ± 1 SD
A	0.50 ml Ra MAFP	20.6 ± 2.4	0.440 ± 0.247*
B	0.25 ml Ra MAFP	20.0 ± 0.0	0.524 ± 0.124
C	0.50 ml non immune RIgG	19.5 ± 1.7	0.666 ± 0.144
D	0.25 ml non immune RIgG	19.8 ± 1.8	0.522 ± 0.246
E	0.50 ml PBS	19.2 ± 3.0	0.745 ± 0.194
F	No Treatment	21.3 ± 2.3	0.578 ± 0.228

* Diff. from E at P > 0.05 but not from F.

TABLE 3. *Tissue Distribution of Radioactivity After Clearing Circulating AFP and Injecting Radiolabeled Anti-AFP, and Normal IgG in C57/LJ Mice Bearing BW 7756 Hepatomas*

	Day 1				Day 3				Day 5			
	% Dose/Gram		Tissue: Blood Ratio		% Dose/Gram		Tissue: Blood Ratio		% Dose/Gram		Tissue: Blood Rati	
Tissue	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG
Tumor	11.87	9.54	.69	.72	7.48	5.40	.66	.69	2.66	2.81	.73	.86
Blood	17.11	13.28	—	—	11.26	7.83	—	—	3.62	3.26	—	—
Liver	4.51	2.46	.26	.18	1.93	1.58	.17	.20	0.37	0.31	.10	.10
Spleen	2.49	1.96	.14	.15	1.99	1.70	.18	.22	0.27	0.21	.07	.06
Kidney	6.07	3.98	.35	.30	2.58	2.16	.23	.28	0.21	0.53	.06	.16
Lung	7.83	6.08	.46	.46	3.54	3.60	.31	.46	0.84	0.72	.23	.22
Heart	5.65	3.67	.33	.28	2.60	3.84	.23	.49	0.10	0.27	.10	.08
Bladder	13.41	8.24	.78	.62	7.43	6.21	.66	.79	0.52	.39	.14	.12

sue in concentrations two to four times greater than those observed for control IgG (Table 4). Such localization did not occur if a larger tumor mass was present (tumors were moderate size by our definition), regardless of whether or not an AFP clearing dose of 0.5 ml of anti-AFP$_1$ was given prior to administration of labeled anti-AFP$_2$ (Table 5). In cleared animals with small tumors, the tumor:blood ratio of specific activity increased with time and reached levels consistent with detection of tumor by photoscanning.[4] The tumor:blood ratio of isotope activity was found to be greater than 6:1 by the sixth post injection day, and therefore within the range suggested as necessary to localize therapeutic amounts of radioactivity.[2] In this series animals were not followed for a period sufficient to observe any possible anti-tumor effects of the labeled antisera.

Discussion

The studies reported here demonstrate that AFP production by human and murine hepatomas can be readily detected and quantitated and that serum levels are related to tumor growth. Resection of hepatoma tissue or effective chemotherapy or radiotherapy causes reduction of serum AFP levels and conversely increasing AFP levels signal recurrent or progressive disease.

The failure to identify the initial site of recurrent malignancy in J. B. (Fig. 2) by selective venous sampling and quantitation of tumor antigen was disappointing. Such situations will only increase in frequency as the use of blood tests for cancer detection increases. Unfortunately the several day half life of these antigens results in a rate of metabolic turnover so slow that elevated antigen levels do not develop in the venous blood draining areas of tumor involvement and residual or recurrent disease escapes detection.

The administration of a single dose of anti-AFP can reduce to zero or "clear" significant AFP titers for an 8–10 hour interval. Thereafter, a state of AFP excess again develops unless repeated doses of anti-AFP are administered. Repeated doses of antisera in animals wit a small tumor load will maintain a state of antibod excess for a significant period, and the doses used i this study maintained such a "cleared" state for eight da after tumor inoculation. However, our studies fail t support the previous finding that repeated injectio of anti-AFP suppress tumor growth or result in hist pathology suggestive of tumor injury.[8] In the prese study, there was a small but not statistically significa difference in the weight of tumors in animals receivin anti-AFP as compared with various control injection No differences were noted in the tumor histology. T findings of little or no significant difference in tum weights and histology after 14 days of treatment wit anti-AFP$_1$ together with the detection of a rapid elev tion of circulating AFP levels suggested further trea ment with anti-AFP alone was unlikely to be effectiv

The initial attempt to utilize anti-AFP as a carri with which to localize selectively significant amoun of isotope in hepatoma tissue failed because the amou of anti-AFP antibody (anti-AFP$_1$) was low in relati to the amount of labeled but indifferent IgG. Howeve anti-AFP antibody concentrated by precipitation wi the specific antigen and dissociated from it by acidific tion and sephadex column purification (anti-AFP$_2$) di

TABLE 4. *Tissue Distribution of Radioactivity Three Days Af Clearing Circulating AFP and Injection of Radiolabeled High Specificity Anti-AFP$_2$ and Normal IgG into C57/LJ Mice Bearing BW 7756 Hepatomas*

	% Dose/Gram		Tissue: Blood Rati	
Tissue	AntiAFP	IgG	AntiAFP	IgG
Tumor	8.42	5.48	1.65	0.57
Blood	5.105	9.61	—	—
Liver	0.94	1.42	0.18	0.15
Spleen	0.84	1.06	0.16	0.11
Kidney	1.34	2.12	0.26	0.22
Lung	1.72	2.94	0.34	0.31
Heart	0.84	1.50	0.16	0.16
Bladder	2.97	5.20	0.58	0.54

TABLE 5. *Tissue Distribution of Radioactivity Three Days After Injection of Radiolabeled High Specificity Anti-AFP and Normal IgG into (a) Cleared Animals with Small Residual Tumor (b) Cleared Animals with Large Residual Tumor and (c) Uncleared Animals with Large Tumors*

	Cleared Animals, Small Tumor				Cleared Animals, Large Tumor				Uncleared Animals, Large Tumor			
	% Dose/Gram		Tissue: Blood Ratio		% Dose/Gram		Tissue: Blood Ratio		% Dose/Gram		Tissue: Blood Ratio	
Tissue	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG	AntiAFP	IgG
Tumor	8.42	5.48	1.65	0.57	0.34	5.38	0.62	0.58	.75	7.37	.39	.67
Blood	5.10	9.61	—	—	0.55	9.23	—	—	1.92	10.94	—	—
Liver	0.94	1.42	0.18	0.15	0.12	1.34	0.22	0.14	.26	2.37	.14	.22
Spleen	0.84	1.06	0.16	0.11	0.26	1.16	0.47	0.13	.25	2.20	.13	.20
Kidney	1.34	2.12	0.26	0.22	0.20	2.27	0.36	0.24	.39	3.35	.20	.31
Lung	1.72	2.94	0.34	0.31	0.20	3.08	0.36	0.33	.31	4.76	.16	.44
Heart	0.84	1.50	0.16	0.16	0.08	2.17	0.14	0.24	.17	2.45	.09	.22
Bladder	2.97	5.20	0.58	0.54	0.26	5.36	0.47	0.58	.58	5.71	.30	.52

localize significantly in hepatoma. Hepatomas exposed to anti-AFP$_2$ contained threefold the amount of radioactivity found in hepatomas exposed to normal IgG while the activity found in other tissues did not differ significantly.

Conceptually, the only uncertainty in considering the AFP/hepatoma system as a model for humoral immunotherapy of solid tumors is the secretory nature of AFP which is manufactured in cytoplasm and secreted into the extracellular fluid about tumor cells. However, a state of antigenemia may exist for all malignancies whether because of secreted antigen or cell breakdown with membrane antigen release and hence conclusions reached in studying this model may prove generally applicable.

The administration of heterologous antisera to patients with tumor associated antigenemia may potentially cause a variety of diseases mediated by antigen antibody complexes, which may limit the duration of treatment and the amount of antisera administered. Further the use of even highly purified labeled antibody in animals having large tumors failed to localize radioactivity in the tumor even though the animals were initially cleared of circulating antigen. This may have occurred because the rate of antigen synthesis exceeded the rate at which antibody was administered. In the case of the hepatoma studied, enormous quantities of whole antisera (2–4% total body weight) were necessary to clear, even transiently, circulating tumor antigen. Thus, in evaluating the potential of humoral anti-cancer therapy the kinetics of tumor antigen synthesis and release become extremely pertinent. A large tumor, secreting antigen at a rapid rate, is likely to require prohibitive amounts of purified antibody before circulating tumor antigen is cleared and antibody selectively localized in tumor tissue. However other malignancies may not release large amounts of tumor associated antigen, particularly if the antigen is related to structural cellular component rather than embryonic secretory products. Equally germane and a second problem for immunotherapy is the development of purified anti-tumor antibody from animals inoculated with tumor determinants on structural components. Currently under these circumstances many antibody specificities are produced and the need for extensive absorptions limits the quantity of antibody obtained. Thus, there is a clear contrast between the AFP/hepatoma system where large amounts of antibody can be obtained, but may be rendered ineffectual by secretory antigen, and other tumor systems where meager amounts of specific anti-tumor antibody are prepared with difficulty, but may prove more effective.

Irrespective of the tumor systems studied antitumor antibody will localize specifically in tumor tissue only when certain criteria are fulfilled: 1) a stage of minimal residual tumor mass is obtained; 2) circulating tumor associated antigen is cleared; 3) the antisera used is of high affinity, specificity and concentration; 4) antibody excess is maintained for significant periods; and 5) a reliable assay system is utilized for recognition of the above conditions.

Acknowledgment

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DISCUSSION

Dr. Elton Watkins, Jr. (Boston): I have enjoyed this elegant presentation not only because it indicates unique methods of diagnosis and treatment of hepatoma, but also because it represents another example of a rather general derangement of serum alpha-globulin metabolism in patients with cancer. The general phenomenon may have bearing on this study, and this study may have bearing on the general phenomenon.

In general the alpha-globulins are glycoproteins. One of their characteristics is the presence of a highly-acid pyranose sugar, sialic acid, in the terminal position in the sugar prosthetic group. The sialic acid has immunological effects which have been studied in pioneer reports by members of this society such as MacBeth and Mannick.

If we take a series of patients with common solid tumors (slide) and measure the concentration of sialic acid bound to their serum proteins as a measure of alpha-globulin level, we find that patients with resectable tumors have a significant elevation of bound sialic acid and that terminal non-resectable patients have an even higher level. Thus the serum bound sialic acid level is related to the tumor load. Although this effect is not specific for cancer, I should point out that the simple chemical test may be of some use in monitoring the course of malignancy without complicated immunological techniques.

These sialoproteins in general tend to regulate the intensity of cell mediated immune response. The presence of the sialoprotein in the cancer cell membrane, for example, tends to enable these cancer cells to escape from immunological surveillance as has been so well documented by Dr. Simmons.

(Slide) If we isolate blood lymphocytes from patients with common solid tumors and culture the lymphocytes with tumor cells that have been pretreated with an enzyme, neuraminidase, that removes the sialic acid from the cell membrane, then a violent lymphoblastic response is produced in a preponderance of the patients. This reaction may equal or exceed the response to entirely foreign allogeneic activator cells from another person. In contrast, the lymphocytes do not recognize and respond to the intact cancer cell before the sialic acid has been removed.

If one adds to such a culture, blood serum from the patient or another patient with malignancy, there is blocking of the lymphoblastic transformation. The degree of blocking is proportional to the concentration of bound sialic acid in the serum added to the culture. A patient with a normal bound sialic acid level or alpha-protein level will present no block and a patient with a high level will have a complete block of lymphoblastic response. Enzymatic removal of sialic acid from the blocking protein will eliminate the block.

One specific point relative to this elegant paper is that glycoproteins of this type are generally poor immunogens due to the presence of the sialic acid. Removal of sialic acid by enzyme or gentle acid hydrolysis may make a protein such as alpha-fetoprotein much more immunogenic while retaining the specificity of the immunological reaction.

I would like to ask Dr. Parks: Did you observe nephrotoxic changes in view of the well known effects of antigen-antibody complexes on the kidney, and in this instance, radioactive antigen-antibody complexes? Such a nephrotoxic effect might interfere with this method as a form of therapy.

Dr. Donald Lee Morton (Los Angeles): The significance of this presentation can be briefly summarized as follows. Not only hepatomas but probably all types of tumors secrete unique antigens such as alpha fetoprotein into the blood plasma. The quantity of these circulating tumor associated antigens in the serum are a reflection of the size of tumor burden in the host and can be used to monitor tumor therapy as so beautifully demonstrated by the authors. Furthermore, antibodies highly specific for these tumor associated antigens can be labelled with radioactive isotopes or cytotoxic substances such as diphtheria toxin and the antibody can serve as lethal missile to carry the toxin directly to the tumor cell.

Another application of this aspect of tumor immunology involves diagnosis and staging of malignant disease. It is likely that the specificity of some of these circulating tumor antigens will be such that the presence of these abnormal antigens in the sera will indicate which patient has a hidden malignancy in their body. But where is the malignant tumor located? It is possible by the use of specific radio-labelled antibodies and radio-isotopic scanning devices to determine the exact location of the neoplasm For example in a women suspected of having breast cancer because she has a specific breast tumor antigen in her serum, one may determine by radio scanning techniques, not only the involved breast but which quadrant of the breast has the hidden neoplasm. Although such applications of tumor immunology to cancer diagnosis and therapy are not possible at the presen time, it is likely that these techniques will be clinically applicable within this decade.

In closing, I would like to offer to the authors a possible explanation for the low level of localization of specific antibodie in the tumor as compared to normal tissues. Since they pretreated the mice with unlabelled antibody to clear the circulating alpha fetoprotein from the serum prior to the administration of labelled antibody, it is likely that they were getting competitive inhibition of the unlabelled antibody with the radio-labelled antibody fo the antigen sites on the tumor cell surface. Thus, the concentration of labelled antibody in the tumor tissue was not as grea as it might have been.

Dr. Jonathan E. Rhoads (Philadelphia): I would like to cal attention to another method of detecting primary hepatoma, by the measure of 5 nucleotide phosphodiesterase isoenzyme. This i done in serum by gel electrophoresis. It's a method developed by Dr. K. C. Tsou and his associates, S. Ledis and Dr. M. McCoy. In the experience of Tsou, McCoy and Lo, it is a bit more sensitive They have 88 positives in 43 hepatomas, but it is less specific in that it's apt to be positive also in metastatic carcinoma of the liver

Therefore, it would be less useful for diagnosis of primary hepatoma but it could also be used for following the effects o chemotherapy in metastatic carcinoma of the liver.

I'm particularly glad that Dr. Parks emphasized the role o surgery in reducing tumor burden, as I think this will emerg as more and more important. And, indeed, I think we may as ourselves whether that isn't what we have been doing in a grea many of the cases in which we have thought we were excising th whole thing.

A study of late recurrences pushes one toward the view tha perhaps we don't actually very often have the chance of completely encircling and excising the tumor before it has all spread but that what we do accomplish is to beneficially influence th balance between tumor aggression and host resistance.

A Decade Followup in Early Cases of Renal Homotransplantation

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Sixty-four consecutive patients underwent renal homotransplantation 10 1/6 to 11½ years ago, 46 from related and 18 from nonrelated living donors. Thirty-six of these recipients were alive when this series was presented to the American Surgical Assocation in 1965. Now, nine years later, 26 (72%) of the 36 still survive, in 22 instances with function of their original grafts. The 10 who died in the interim tended to have subnormal renal function or graft failure. However, the actual causes of death included 2 or more examples each of myocardial infarction, hepatitis, or other systemic infections. The prognosis for achieving a one decade survival was not obviously related to HL-A tissue match. The best results were with related kidneys, within which subgroup 24 (52%) of the original recipients are still alive. However, there was no particular category of consanguineous donor that had a marked superiority. Only 2 of 18 nonrelated recipients are still alive. All 36 patients who were alive in 1965 had a biopsy of their renal homograft. Kidneys that were destined to function for a decade tended to have relatively minor histopathologic abnormalities. If serious glomerular lesions were found, the outlook for long graft survival was grave. Vascular lesions had a somewhat less serious import. Mononuclear cell infiltration, tubular atrophy, and interstitial fibrosis proved prognostically to be the least significant. Long-term followup of these early cases has shown the durability of chronic renal homografts, particularly if these are from related donors, and has demonstrated the very high degree of rehabilitation that could be achieved even in the early days of renal homotransplantation.

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At the May 1965 meeting of the American Surgical Association a report[24] was given on 64 consecutive renal homograft recipients treated at the Colorado General and the Denver Veterans Administration Hospitals. Thirty-six of these patients were still alive 13½–30 months postoperatively.

The climate between November 1962 and March 1964, when the series was compiled, had overtones of anxiety as well as excitement. Because the degree of success being achieved had not been anticipated by basic immunologists and for that matter was not yet generally appreciated by clinicians, expressions of criticism and concern were common.[3] Even those aware of the encouraging statistics of 1962–1963 conceded that the ultimate prognosis of the renal recipients still living was not predictable, since only very isolated examples of long-term survival had been recorded before this time.[8,11,13–15,22]

With the passage of nine more years, followups exceeding a decade are now available for the 26 patients who still survive from the early Colorado series of 1962–1964. Using the data of the American College of Surgeons Transplant Registry for a reference, these residual 26 patients account for about half of those in the world who were treated before March 1964 with renal homotransplantation and who remain alive today. Thus a description of their fate may serve as a bellweather for recipients treated in subsequent years who have been followed for briefer periods.

Methods

The 64 cases have been described elsewhere in great detail, including surgical techniques and management.[23] Transplantation was from related donors in 46 instances, including 23 siblings, 20 parents, one aunt, one uncle, and one cousin. The other 18 donors were normal healthy volunteers. In six of the 64 cases, there was immediate or very early failure of an initial homograft which was promptly removed. A second kidney was provided 6–47 days after the original operation. In the foregoing description of organ source and

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in subsequent remarks only the second or definitive donor for these six recipients is considered.

Typing procedures were not available when this series was compiled. After Case 23, the kind of red blood cell type incompatibility that can lead to hyperacute rejection[23] was avoided. Otherwise, the donor-recipient matching was not by any kind of immunologic guidelines. Parenthetically, one of our earliest recipients (LD 2) is still alive with perfect graft function eleven years and three months after transplantation from a B+ red cell type donor to an A+ type recipient, a combination which would no longer be used.

Between 1964 and 1970, retrospective HL-A typing was performed by Terasaki of Los Angeles on surviving recipients and their donors.[26] As a consequence, a statement about the quality of HL-A match can be made for the last 36 survivors. This was expressed as a letter histocompatibility grade. An A match indicated identity of the measured donor and recipient HL-A antigen groups. With a B match, no incompatibilities were present, but there were one or more examples of non-identity or else nonconformity of unclassified antigens. C and D-E matches were progressively less satisfactory with frank mismatches of one, two or more antigen groups. Because new HL-A groups were discovered and characterized throughout the period of analysis, the basis for grading was more complete and consequently more accurate at the end of the study than at the beginning.

Immunosuppression was with the double drug combination of azathioprine and prednisone. Two regimens were used.[23,25] In 45 cases azathioprine was started alone; prednisone was added in 43 of these 45 patients with the appearance of clinically obvious rejection. In the other 19 recipients both drugs were administered from the outset. Actinomycin C and local homograft irradiation were employed irregularly.

All 64 recipients had splenectomy. The first eight, of whom four are still alive (LD 1, 2, 3, 6) had pretransplantation thymectomy; patient LD 1 has undergone retransplantation. Nine additional patients had thymectomy 8½–17 months after transplantation in the hope of being able to reduce immunosuppression (LD 13, 15, 22, 30, 40, 41, 47, 50, 54). Five of the latter nine recipients are still alive but two are dependent upon retransplanted kidneys and a third one is presently anephric. Although thymectomy may have a subtle long-term immunosuppressive effect in adult humans,[26] it is no longer performed at our institution either before or after transplantation.

Between 21 and 26 months postoperative, 35 of the 36 patients living in 1965 had open homograft biopsy; the thirty-sixth graft (LD 44) was retrieved by homograft nephrectomy after 60 months. In seven cases, it was possible to compare two-year biopsies with the same kidney retrieved 2½–7 years later at autopsy or homograft nephrectomy. Invariably the same abnormalities were present both times but were more advance on the later occasion.

All the tissues were examined by light microscopy Sections were cut at both 5 μ and 0.5 μ. The forme were stained with hematoxylin and eosin, periodic aci Schiff (PAS), Weigert's for elastic counterstained wit hematoxylin and van Gieson, and methyl green pyronin The 0.5 μ thick sections were stained with Azur 2.

Electron microscopy was carried out on all of th specimens. The tissue from biopsies was primarily fixe in Palade's buffered osmium tetroxide and embedde in Epon 812. Autopsy material was fixed in buffere formalin and then post-fixed in osmium tetroxide. Ultrathin sections were stained with lead citrate and examined in a Phillips 300 electron microscope.

From 27 of the homografts, samples of tissue wer frozen in liquid nitrogen and stored at −70 C unti examined. Sections 4 μ thick were cut in a cryostat an stained with fluorescein conjugated antisera. The fluorescent reagents used were antisera made in rabbits an goats to human IgG, IgM, fibrinogen, C'lq and β1C/β1 globulin. Specificity of the antisera was confirmed befor application to the tissue by immunoelectrophoresis an double diffusion in agarose. Specificity of the fluorescence was established by blocking positive reaction with unconjugated antisera, by absorption of the labelle antisera with specific antigens, and by the use of a antihuman serum albumin control.

Using light microscopic and ultrastructural analysis the presence or absence of the following features wa determined in the homografts: 1) subendothelial glomerular capillary basement membrane thickening; 2) subepithelial glomerular capillary basement membran thickening; 3) increased cellularity of the glomerula tufts; 4) increased amount of mesangial matrix; 5 tubular atrophy; 6) interstitial fibrosis; 7) mononuclea cell infiltration of the interstitium; 8) "hyaline" in th ateriolar walls; and 9) thickening of the intima of th interlobular arteries. In addition, the frozen tissues wer used to determine deposits of IgG, IgM, complemen or fibrinogen in the glomeruli. The lesions and deposit were graded in severity from 0 to 4.

Eventually, the Glomerular Categories 1–4 were combined and averaged to reach a summary score of th magnitude of abnormalities (glomerular index); th immunofluorescence examinations were always roughl confirmatory of the morphologic scores. The grades f all nine microscopic categories were averaged for a overall "pathologic index." The ultimate fate of thes kidneys was correlated with the various pathologi lesions.

In 33 of the 36 cases, the patients' own diseased kidneys were examined and the findings were ultimatel compared to those in the homografts. These specimen were all studied by light microscopy and in a fe instances by immunofluorescence and/or electronmicroscopy.

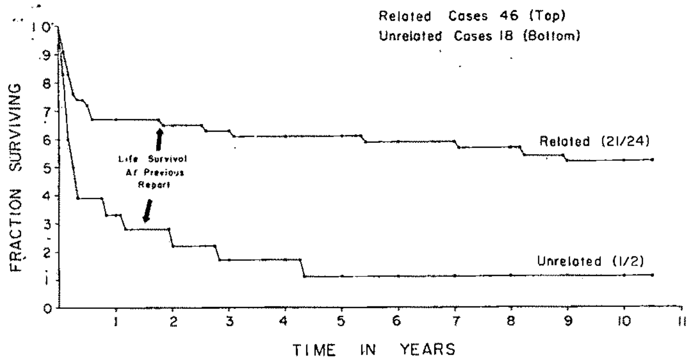

FIG. 1. The life survival curves of 64 patients treated by renal transplantation between the autumn of 1962 and March 1964. These cases were reported to the American Surgical Association in May 1965, at which time the life survival curves had evolved to the points indicated by the black arrow. Note that 72% of the survivors of 1965 are still alive 9 years later. The denominators in parentheses indicate the number of living recipients and the numerators indicate the original homografts that are still functioning.

Results

Survival

Related Cases. By May 1965, 15 of the 46 related recipients had died, leaving a residual group of 31 (Fig. 1). At the three-, five- and ten-year marks, the recipients remaining numbered 29, 28 and 24 respectively. There are 24 or 52% of the original 46 who are still alive after 10⅙–11½ years. No one of the survivors is now on dialysis. Twenty-one of the 24 have function of their original grafts. The other three underwent retransplantation (Table 1) when their original kidneys failed after 5½ years (LD 1), 6 years (LD 41) and 5 years (LD 50). Second grafts from the other parent have functioned satisfactorily for 6 years in Patient LD 1 and 4½ years in LD 50. The third patient (LD 41) has had four cadaveric retransplantations. The first three of these grafts underwent hyperacute, acute, or delayed rejection. The final kidney has been functioning satisfactorily for 16 months.

The survival in the consanguineous cases was not strikingly influenced by the nature of the relationship (Table 2). After parent-to-offspring transplantation, 14 of 20 recipients (70%) were alive at the end of six months. By 10⅙–11½ years there were still 13 (65%) alive, although three of these have undergone retransplantation. Also of interest was the fact that all of the three distantly related renal grafts (aunt, uncle, and cousin) were providing stable function more than a decade after their insertion (Table 2). The greatest attrition was of sibling recipients (Table 2), amongst whom a 61% one-year survival had eroded to 35% after a decade.

Nonrelated Cases. By May 1965, only five of the 18 nonrelated recipients were still alive (Fig. 1). In the intervening nine years, three more have died leaving only two. One of these two recipients who is now ten years, two months, probably has the longest continuously functioning unrelated homograft in the world. The second surviving patient lost his unrelated graft after a little more than two years (LD 54). He underwent successful retransplantation with his mother's kidney in September 1966 (Table 1). After six years of essentially normal function, he became mentally depressed and discontinued all immunosuppression. After five or six months the maternal kidney failed. He was returned to chronic hemodialysis and is awaiting a cadaver organ.

Causes of Late Death. The ten patients who died between 1965 and 1974 included seven recipients of related grafts and three recipients of unrelated organs; five of them (LD 15, 18, 36, 47 and 48) had life-sustaining although subnormal function of their original grafts from one-and-three-quarters to nine years postoperatively (Table 3). The deaths of two of these five patients were caused by acute myocardial infarction (LD 18 and LD 48). A third patient who died almost nine years after transplantation (LD 15) had moderately severe chronic aggressive hepatitis which was first diagnosed eight years earlier; in addition, the immediate cause of death was acute hemorrhagic pancreatitis. The two other patients who died with functioning original kidneys (LD 36 and 47) had multiple infections (Table 3).

One of the other five patients died after he was placed back on dialysis but before retransplantation could be considered (LD 45). He had a cardiac arrest just at the conclusion of a dialysis treatment.

The other four patients had attempts at retransplantation which were followed by a variety of lethal complications (Table 3), including suicide, perforated sigmoid diverticulitis and bronchopneumonia. The longest sur-

TABLE 1. *Four Patients Alive After One or More Late Retransplantations*

LD Number	Date First Transplantation	Original Donor	Date Retransplantation(s)	Retransplant Donor	Present BUN mg%	Present Ccr ml/min	Present BP mml/Hg	Prednisone mg/day	Total Survival Years
1	11/24/62	Mother	5/21/68	Father	18	60	100/70	15	11.4
41	11/23/63	Mother	1/22/70 6/29/70 2/27/71 12/29/72	Cadavers	29	40	124/90*	25	10.4
50	1/25/64	Father	11/7/69	Mother	29	48	120/85	14	10.3
54	2/24/64	Unrelated	9/26/66	Mother	Anephric for 1 1/2 yrs.			0	10.2

TABLE 2. *Influence of Consanguinity Upon Present Survival in 46 Related Cases, 10 1/6–11 1/2 Years Later*

	1 Year		3 Years		5 Years		Now	
Donor	Patient	Graft	Patient	Graft	Patient	Graft	Patient	Graft
20 Parents	14	14	14	14	14 (70%)	14 (70%)	13 (65%)*	10 (50%)
23 Siblings	14	14	12	12	11 (48%)	11 (48%)	8 (35%)	8 (35%)
3 Aunt, Uncle, or Cousin	3	3	3	3	3 (100%)	3 (100%)	3 (100%)	3 (100%)

* Retransplantation was carried out after 5 1/2, 5 3/4, and 6 1/6 years.

viving patient (LD 40) died of hepatic failure secondary to chronic aggressive hepatitis, Australia antigen positive, 18 months after successful cadaveric retransplantation and eight years, two months after the original transplantation.

Renal Function, Blood Pressure and Immunosuppression

The current renal functions of the four survivors who have undergone retransplantation is shown in Table 1. Table 4 contains the functions from 22 primary kidneys that have functioned for 10⅙ to 11½ years. On the average, the function of the organs is superb. Only one of the original grafts is distinctly subnormal.

The average daily doses of prednisone are small enough so that only one of the 26 patients (the most recent retransplant) has a Cushing's facies. There are no examples of steroid-induced diabetes. Most of the patients have had stable azathioprine doses for years.

Over the years, we have had a number of patients discontinue immunosuppressive treatment, usually because of indifference to the tedium of following a therapeutic schedule. One of the chronic survivors (LD. 49) in this early series discontinued all medications about 14 months ago without any untoward effect to date. Another recipient (LD 3), who also was brain-damaged from a stroke prior to transplantation, has become an alcoholic in the 11¼ years of survival. This patient who has never required prednisone probably discontinued has azathioprine in 1970 or 1971.

Arterial hypertension is an almost universal finding in the immediate posttransplantation period and even for several years afterwards.[26] With longer followup, only one of the 25 survivors who has renal function (and this the retransplant recipient of 16 months ago) has severe hypertension. Four other patients receive small daily doses of antihypertensives. The other recipients require no antihypertensive therapy.

The Influence of HL-A Match

Among the 36 patients alive in May 1965, the quality of the HL-A match did not profoundly influence the durability of the homografts in the succeeding nine years (Tables 4, 5).

The Incidence of Malignancy

Neoplasia was not diagnosed in any of the 28 patients who died before May 1965, after survivals that had ranged from a few days to more than 13 months. Six (17%) of the 36 recipients who remained alive at that time developed malignant lesions at some time during the ensuing nine years. These tumors all originated in the skin and were all successfully treated with conventional means. The features of these carcinomas are summarized in Table 6.

Rehabilitation

The social and vocational rehabilitation amongst the 26 present survivors has been very nearly complete.

TABLE 3. *Cause of 10 Deaths Occurring Since May, 1965*

			Kidney Function Just Before Death				
LD No.	Age at First Transplant	Patient Survival	BUN (mg%)	Cr (mg%)	Ccr (ml/min)	Cause of Death	Time Retransplantation Before Death
15	23	8 yr., 11 mo.	70	2.5	30	Pancreatitis Chronic aggressive hepatitis	No
18	39	2 yr., 6 mo.	32	1.6	60	Myocardial infarction	No
27	20	2 yr., 9 mo.		Failed Kidney		Bronchopneumonia	1 Month
30	40	4 yr., 3 mo.	25	1.6	15	Perforated sigmoid diverticulitis	2 Months
36	43	1 yr., 11 mo.	50	1.5	30	Systemic CMV infection Chronic aggressive hepatitis Sacral cellulitis	No
40	21	8 yr., 2 mo.	60	1.4	40	GI bleeding Chronic aggressive hepatitis Hepatic failure	18 Months
44	48	5 yr., 4 mo.		Failed Kidney		Suicide by refusing dialysis	2 1/2 Months
45	35	3 yr., 1 mo.		Failed Kidney		Cardiac arrest while on dialysis	No
47	37	1 yr., 9 mo.	65	3.5	10	Aspergillus pneumonitis Pneumocystis carinii Fatty infiltration of liver Systemic CMV infection	No
48	34	7 yr., 3 mo.	60	3.0	15	Myocardial infarction	No

TABLE 4. *Data on Primary Homografts*

LD No.	Date Op	Donor	HL-A Match	BUN	Ccr (ml/min)	BP	Azathioprine mg/day	Prednisone mg/day
1	11/24/62	Mother	C	†	†	†	†	†
2	1/31/63	Sister	A	19	70	120/80	100	0
3	2/9/63	Brother	A	11	133	110/70	150	0
6	4/17/63	Brother	D	12	90	115/90	200	10
12	6/7/63	Brother	B	20	68	140/90	100	15
13	7/3/63	Mother	D	17	70	106/50	87.5	7.5
14	7/5/63	Brother	B	12	120	130/90	150	0
15	7/8/63	Brother	B	‡	‡	‡	‡	‡
17	7/19/63	Mother	B	10	64	130/95	100	2.5
18	7/24/63	Sister	D	‡	‡	‡	‡	‡
22	8/12/63	Mother	B	25	80	115/80	137.5	5
25	8/21/63	Brother	C	18	80	110/70	50	10
27	9/3/63	Unrelated	D	‡	‡	‡	‡	‡
30	9/30/63	Unrelated	D	‡	‡	‡	‡	‡
33	10/7/63	Mother	B	14	85	130/80	125	0
34	10/11/63	Mother	C	13	60	110/75	50	0
36	10/14/63	Unrelated	B	‡	‡	‡	‡	‡
37	10/18/63	Mother	C	24	80	120/80	75	15
39	11/13/63	Mother	C	23	65	115/80	125	10
40	11/16/63	Mother	A	‡	‡	‡	‡	‡
41	11/23/63	Mother	C	†	†	†	†	†
42	11/27/63	Father	D	24	70	110/70	125	7.5
44	12/7/63	Sister	A	‡	‡	‡	‡	‡
45	12/10/63	Sister	C	‡	‡	‡	‡	‡
47	1/4/64	Brother	B	‡	‡	‡	‡	‡
48	1/10/64	Sister	A	‡	‡	‡	‡	‡
49	3/3/64	Sister	B	15	70	110/70	0	0
50	1/25/64	Father	C	†	†	†	†	†
51	2/10/64	Aunt	E	17	68	90/75	125	10
52	2/17/64	Father	B	14	90	140/60	150	7.5
53	2/22/64	Uncle	C	26	57	90/60	100	5
54	2/24/64	Unrelated	C	†	†	†	†	†
55	2/26/64	Father	C	30	40	120/80	150	15
58	3/13/64	Sister	A	16	98	120/80	125	10
60	3/17/64	Cousin	D	59	35	150/110	62.5	25
63	3/27/64	Unrelated	B	26	90	130/90	125	12.5

1 = Subendothelial glomerular capillary basement membrane thickening.
2 = Subepithelial glomerular capillary basement membrane thickening.
3 = Increased cellularity of glomerular tufts.
4 = Increased amount of mesangial matrix.
5 = Tubular atrophy.
6 = Interstitial fibrosis.
7 = Mononuclear cell infiltration of the interstitium.
8 = "Hyaline" in arteriolar walls.
9 = Thickening of intima of interlobular arteries.
0 = No glomerular lesions compatible with glomerulonephritis
NO = Impossible to be transmission of glomerulonephritis because original disease in no way immunological.
NO = Very unlikely to be transmission because original disease chronic pyelonephritis.
(NO) = Unlikely to be transmission, but possible because original disease glomerulonephritis.

All 14 of those who were adults (18 or older) at the time of transplantation are employed, frequently in jobs for which they were specifically trained postoperatively. Twelve of the survivors were "pediatric" patients (ages 3–17). The three-year-old who is now almost 14 is a healthy, but physically stunted school boy. The other 11 have reached adulthood and are college students or job holders. Our patient who was a 21-year-old unskilled brain-damaged student is now a 32-year-old alcoholic day field worker.

Three of the patients who were adolescents at the time of transplantation developed necrosis of one or both of the femoral heads during the early postoperative period. Two of the three learned to walk adequately despite this handicap. The third had bilateral total hip replacement performed successfully nine years post-transplantation.

Eleven of the 64 patients of the original series have had children after transplantation. Two of these parents who were female have had three children and the nine male parents have fathered 13 children. One of the offspring of a male patient (LD 63) had a meningomyelocele which was surgically repaired. None of the patients who became parents during the post-transplantation period has died.

*of 36 Renal Recipients.**

Time Biopsy (Months)	1	2	3	4	Glomerular Index	5	6	7	8	9	Overall Pathologic Index	Original Diagnosis	Glomerular Nephritis in Transplant	Time Primary Graft Function (Months)	Time Patient Survival (Years)
24	2	0	2	1	1.25	2	1	2	1	2	1.44	CPGN	(T)	65	11.4†
24	0	0	0	0	0	0	0	0	0	0	0	CPGN	0	135	11.3
24	2	0	0	0	.5	0	1	0	0	0	.33	CLGN	(NO)	134	11.2
23	0	0	0	0	0	0	1	0	0	0	.11	CPGN	0	132	11
22	0	0	0	0	0	2	2	1	1	3	1.0	RPGN	0	131	10.9
21	0	0	0	0	0	1	1	3	1	1	.78	CPGN	0	130	10.8
21	0	0	0	0	0	1	1	1	2	0	.55	Unknown	0	130	10.8
21	1	0	0	0	.25	1	1	1	1	1	.67	CPGN	(NO)	107	8.9‡
26	0	0	0	0	0	1	1	1	0	1	.44	CPYN	0	129	10.7
26	2	0	0	2	1.0	2	2	2	2	2	1.56	CMGN	(NO)	30	2.5‡
25	1	0	0	0	.25	1	2	1	0	2	.78	POLY	NO	129	10.7
24	0	0	0	0	0	0	1	1	0	0	.22	Unknown	0	128	10.7
24	3	0	2	2	1.75	1	1	1	1	3	1.56	CPGN	(T)	31	2.8‡
24	3	0	1	2	1.5	3	3	3	3	3	2.33	CMGN	T	48	4.3‡
23	0	0	0	0	0	0	0	0	0	0	0	CPGN	0	127	10.6
23	0	0	0	0	0	0	1	1	0	1	.33	CPGN	0	127	10.5
22	2	0	0	0	.5	3	3	1	2	3	1.56	CPYN	*NO*	23	1.9‡
22	0	0	0	0	0	1	1	1	0	1	.44	CPGN	0	126	10.5
22	0	0	0	0	0	1	1	1	0	0	.33	CPGN	0	126	10.5
22	2	0	3	3	2.0	1	1	2	3	3	2.0	CLGN	(T)	77	8.2‡
22	3	0	2	1	1.5	1	1	1	1	2	1.33	CPGN	(T)	73	10.4†
22	0	0	0	0	0	1	1	1	0	1	.44	Unknown	0	125	10.4
60	4	4	2	4	3.5	4	4	2	4	2	3.11	CPGN	T	60	5.3‡
25	3	0	1	1	1.25	1	1	1	2	2	1.33	CPGN	(T)	34	3.1‡
22	2	0	0	1	.75	2	3	2	0	4	1.56	CPGN	(NO)	20	1.8‡
24	2	0	0	2	1.0	1	1	0	0	1	.78	CPGN	(NO)	87	7.3‡
22	1	0	0	1	.5	1	1	0	0	0	.44	CLGN	(NO)	122	10.2
24	1	0	0	0	.25	1	1	1	0	2	.67	CPGN	(NO)	69	10.3†
23	2	0	0	1	.75	1	1	1	3	1	1.11	CPGN	(NO)	123	10.2
23	1	0	0	0	.25	0	1	0	0	1	0.33	CPGN	(NO)	122	10.2
23	1	0	0	0	.25	0	1	1	1	1	.55	CPGN	(NO)	122	10.2
22	4	2	3	3	2.75	3	3	3	2	3	2.89	CPGN	T	27	10.2†
23	1	0	0	1	.5	1	1	1	2	3	1.11	CPGN	(NO)	122	10.2
21	0	0	0	0	0	0	0	0	0	0	0	CPGN	0	122	10.2
22	2	0	0	3	1.25	2	2	2	0	0	1.22	CPGN	(NO)	121	10.1
22	4	0	2	4	2.5	1	2	2	1	1	1.89	CPGN	(T)	121	10.1

(T) = Probably transmission of glomerulonephritis.
T = Almost certainly transmission of glomerulonephritis.
CLGN = Mesangiocapillary chronic lobular glomerulonephritis
CMGN = Chronic membranous glomerulonephritis
CPGN = Chronic proliferative glomerulonephritis
CPYN = Chronic pyelonephritis
POLY = Polycystic disease
RPGN = Proliferative glomerulonephritis with crescents

* Patients were alive when reported in 1965[24] and 26 of them survive 9 years later in 1974. Additional data on the patients who required retransplantation are in Table 1.

† Alive following retransplantations.

‡ Dead.

Histopathologic Correlations

The two-year biopsies were included as part of a report made to the American Surgical Association in 1970.[26] These analyses were accepted as the histopathologic basis for the following correlations.

Overall Pathologic Index. When the nine light microscopic categories at two years were averaged (Table 4) it was found that kidneys having a mean index less than 1.33 had a 87.5% chance of functioning for the ensuing eight to nine-and-one-half years (21 of 24). Two of the three patients whose kidneys no longer function despite a score less than 1.33 died of pancreatitis after 107 months (LD 15) and myocardial infarction after 87 months (LD 48). These kidneys had not failed although they were subnormal in their performance (Table 3). The third patient (LD 50) had a score of 0.50 at two years with homograft failure after five-and-one-half years. She underwent retransplantation. A pattern of sporadic discontinuance of immunosuppression for long intervals was later uncovered.

Ten of the 11 two-year biopsies with an overall pathologic index of 1.33 or greater were eventually lost (91%), after a total functional interval of 23 to 77 (mean 43) months (Table 4). In one case (LD 18), in which the index score was 1.56, the patient had a

TABLE 5. *HL-A Matches of 36 Kidneys Which Were Functioning in May, 1965*

Match*	Primary Kidney Still Functioning	Primary Kidney Failed	Death Without Failure of Primary Kidney
A†	3 (50%)	2	1
B	8 (73%)	2	1
C	6 (55%)	5	0
D-E	5 (63%)	2	1

* Five of the 36 kidneys functioning in May, 1965, were unrelated. The only one still functioning had a B match. One of the 4 unrelated kidneys which failed also had a B match, one was a C and 2 were D-E.

† Five of the 6 A matches were siblings and were thought to represent double haplotype HL-A identity of the donor and recipient.

functioning graft but died of a myocardial infarction 30 months post-transplantation. Nine other grafts either failed and were removed or were functionless in place at the time of the recipients' death. Homograft loss was avoided only in Patient LD 63 who had a two year overall pathologic index of 1.89. Now after ten years and two months, the BUN is 26 mg% and the creatinine clearance is 90 ml/min. During all this time he has not had significant proteinuria. Reassessment of the two-year biopsy did not show any features which explained the atypical subsequent behavior of this damaged graft. It is of interest that this patient was studied in 1966 by Dr. Fritz Bach of Madison, Wisconsin who performed a mixed lymphocyte culture examination with the peripheral blood of the recipient and his donor. Although a clear donor-recipient histoincompatibility was detectable by serologic typing, the recipient lymphocytes no longer underwent blast transformation when exposed to killed donor white cells, although they reacted vigorously to third party lymphocytes. The findings were interpreted as indicating specific acquired immunologic tolerance.[1]

Homograft Glomerulonephritis. When the two-year biopsies were reviewed in 1970,[26] a diagnosis of definite glomerulonephritis in the homograft was made if, by light microscopy, over 50% of the glomeruli showed one or more of the following features: 1) focal or diffuse hypercellularity of the tufts and 2) focal or generalized thickening of the capillary basement membranes. These two basic pathologic changes might, or might not, be accompanied by epithelial cell crescents, by a focal or generalized increase in the amount of mesangial matrix, and by the presence of deposits of immunoglobulins and complement on the glomerular capillary wall.

Glomerulonephritis was considered a possibility if the glomeruli appeared normal on light microscopy but: 1) electronmicroscopy revealed an excess of predominantly non-cellular material on either aspect of the glomerular capillary basement membranes; the material could be of any degree of electron density; and/or 2) immunofluorescence demonstrated deposits of immunoglobulins and complement on the glomerular capillary walls. The deposits could be in a granular, linear or mixed pattern.

Using these criteria, 22 of the 35 renal homografts biopsied at two years were diagnosed as having glomerulonephritis, for an incidence of 63%. All 13 kidneys without glomerular lesions at two years are functioning today, whereas only nine of the 22 kidneys with such lesions continue to support life.

The homograft attrition was even greater when the glomerular lesion in the two year biopsies were thought to either certainly or probably represent transmission of the patient's original disease, as judged by comparison with the histopathology of the destroyed native kidneys. Seven (LD 1, 27, 30, 40, 41, 45 and 54) of the eight homografts carrying the firm two year diagnosis of "transmission glomerulonephritis" failed 27–77 months post-transplantation (average 51 months). An eighth

TABLE 6. *Features of Cancers in Original Colorado Transplant Recipients*

LD No.	Age at Time of Transplant (Years)	Time of Onset After Transplant (Month)	Type of Tumor	Treatment	Outcome	Followup After Initial Diagnosis of Tumor (Month)
6	23	75	Basal cell carcinoma of face	Excision	No recurrence	58
30	40	32	Squamous cell carcinoma of skin of ear	Wide excision	No recurrence; died of perforated diverticulitis	20
48	34	74	Squamous cell carcinomas of forearms, right arm, and scalp	Multiple excisions	Died of myocardial infarction	14
55	21	87	Squamous cell carcinoma of face; pre-auricular lymph node	Excision and skin graft	Eight months later had resection of pre-auricular lymph node metastasis and parotid gland	35
60	21	78	Multiple squamous cell carcinomas both upper extremities, face, right knee, lower lip	Multiple excisions	Recurrences; currently being treated with topical 5FU	43
63	35	66	Squamous cell carcinoma of lower lip	Excision	No recurrence	55

kidney which was not biopsied at two years failed at five years and was found also to have transmission glomerulonephritis (LD 44). The only kidney with the stigmata of transmission glomerulonephritis at two years which still functions after ten years is in Patient LD 63.

The devastating prognostic impact of two-year glomerular lesions upon late graft survival could be seen from the glomerular index which was the average of histopathologic Categories 1–4. If the index was less than 1.00 at two years, renal function at one decade was achieved in 83% (20 of 24). With a glomerular index of ≥1.00, the decade success rate was only 18% (two of eleven).

Next to the glomerular abnormalities, the presence or absence of arteriolar and arterial lesions provided the best prognostic insight (Table 4). Cellular invasion, tubular atrophy and interstitial fibrosis were progressively less reliable. However, all categories of lesions scored higher in the kidneys which eventually failed.

Discussion

In 1962 and 1963, three American[9,16,25] and one European[29] centers were acquiring experience with the drug combination of azathioprine and prednisone for the prevention or reversal of renal graft rejection. The progress and the avalanche of observations that followed had amplified significance because of parallel advances in renal dialysis technology by which preoperative recipients could be resuscitated and held in preparation for transplantation or else maintained postoperatively in the event of homograft failure.

The results from the early days of azathioprine-prednisone therapy were unsatisfactory by present day standards, mainly because of the very heavy death rate during the first postoperative year which was particularly devastating in the nonrelated cases. The marked reduction in the early mortality and the means by which this has been achieved have been recently reviewed.[27] The important collateral issue of the long-term outlook of the patient who has passed through a successful early course is a question which the present communication partly answers.

In 1965, when these cases were brought to the attention of the American Surgical Association, the summary statement was made that ". . . for the present it would seem most reasonable to regard homotransplantation as an effective, but incompletely characterized, form of palliative therapy."[24] Now, nine years later, with 26 (72%) of the 1965 survivors still alive and 22 bearing their original homografts, more optimism than ever seems justified about the lasting qualities of homografts if the donors are related.

Using unrelated donors, late losses occur more frequently. In our experience, improvement in patient survival with the use of unrelated organs under presently employed immunosuppressive regimens, including those using ALG, will require acceptance of a much heavier rate of retransplantation than with consanguineous donors.[27]

The hypothetical Achilles' heel of successful organ transplantation under chronic immunosuppression was once projected to be death from complications of immunologic invalidism. The fallacy of this fear has been demonstrated by the followups in the present report. The survivors have had remarkable long-term rehabilitation, both social and vocational, and most have had a very nearly unrestricted return to society. Except for hepatitis, infection has played no role in the deaths after three years. The increased incidence of *de novo* malignancies in the transplant population is acknowledged to be a penalty for chronic immunosuppression and the consequent partial loss of immunologic competence,[26] but the resulting neoplasms have usually been treatable by conventional means with the notable exception of mesenchymal malignancies.[17]

The greatest risk to life that the transplant recipient faces is late slow deterioration of the homograft and cardiovascular and other complications of the recurrent uremia. The correlations in the present report have shown how the quality of the two year biopsy can predict the functional future of the homografts. In passing, it may be noted that with the possible exception of perfectly matched siblings, neither the biopsies nor the chronic clinical course correlate well with the HL-A match.

In the past, the most prognostically serious stigmata to be found in chronic renal homografts have been thought to be arterial occlusive lesions.[21,23] However, in the cases herein reported, glomerular abnormalities were even more discriminating than the vascular ones. A kidney with serious glomerular pathology at two years, had less than a 10% chance of being functional at a decade.

The meaning of glomerular abnormalities in renal homografts has been the subject of much discussion but two principal mechanisms could contribute. In one instance, the autoimmune disease which destroyed the host kidneys could be recapitulated in the new kidneys, as has been particularly well documented in identical twins.[4] On the other hand, the immunologic events of rejection can probably manifest as glomerulonephritis since glomerulonephritis has been seen after animal transplantation[20,30] or transplantation to humans whose original disease was not autoimmune in nature.[7,19] The probable contribution of both kinds of damage to the loss of transplants has been emphasized by a number of authorities.[2,5,6,10,12,18,28] The prognostic reliability of glomerular pathology is probably as high as it is because it picks up both of the aforementioned main pathways of graft injury. With either recapitulation of the original disease or glomerulonephritis secondary to rejection, the immunologic injury could be produced by fixation of anti-GBM antibodies in the graft or more commonly, lodgement of antigen-antibody complexes in the graft. More precise conclusions about these mechanisms will require identification of the specificity of both antigens and antibodies within grafts by elution and other immunologic techniques.

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DISCUSSION

DR. FOLKERT O. BELZER (San Francisco): We are fortunate enough to have followed one of Dr. Starzl's original patients in San Francisco. This man is now 11 years post operative, has not missed a day of work, and has never been in the hospital since his transplant.

I would like to discuss something that Dr. Starzl has also been interested in and, in fact, he published a paper on this in 1968; namely, how much can we decrease our immunosuppressive therapy in these long-term patients, and can we ever discontinue these drugs completely.

After reading Dr. Starzl's paper, I never had the courage to drop immunosuppression completely, but seven of our patients did this by themselves and the results were disastrous.

Some of these patients, fortunately, came to the followup clinic in time; they had elevated creatinines and were restarted on immunosuppressive therapy. Their renal function improved, although rarely to the pre-existing level; some of these patients lost their kidney.

One of these patients, transplanted by Sam Kuntz at Stanford, was a young woman, seven years postoperative, with a creatinine of 0.9 and taking 10 mg of Prednisone and 100 mg of Imuran. She became pregnant and her obstetrician suggested that she drop her immunosuppressive therapy, which she did without telling us. She delivered a normal child, did well for six months, and then arrived at our hospital with a creatinine of 11. We were never able to reverse the rejection.

I think there are three points to be made from this. First, I do not believe we should drop immunosuppression, even for long standing patients, below a certain level; and in adult patients, we should not drop the Prednisone dose below 10 mg.

Second, we must remember that even long-term patients should be followed for the rest of their lives.

Lastly, we should emphasize to long-term survivors that the three or four little pills they take in the morning are still the difference between life and death.

Dr. Richard E. Wilson: (Boston) I thought it would be of interest to the Association for me to provide a comparable series of patients for discussion of Dr. Starzl's valuable presentation. Dr. Tilney and I recently reviewed the results of renal transplants, exclusive of identical twins, performed at the Peter Bent Brigham Hospital in exactly the same time period, September 1, 1962 to March 31 1964.

Forty such allografts were performed, 19 from living related donors, five from cadaver donors, and six from obligatory unrelated living donors of Matson type of kidney. None of the cadaver or obligatory unrelated donor kidney recipients transplanted during that time period lived the one year maximum, although one patient, transplanted in April of 1962 from a cadaver donor lived for two years on his transplant.

Of the living related donor recipients, therefore, 16 of 19 lived more than one year, or 84%; 8 of 19 lived more than five years, 42%; and 7 of 19 lived more than ten years, 37%.

One patient who lived four years received three kidneys before he died, two of those cadaveric. One patient now living over ten years received a second kidney from a cadaver after five years on his first kidney. He, by the way, was a patient in whom we had tried to stop his prednisone; when we tried to restart it, we could never retrieve the rejecting kidney.

No malignancies developed in any of these recipients. Another patient that I transplanted in Oslo in 1963 from his mother is still alive and well, never having had a rejection in these eleven years.

I think it is interesting that, while a greater proportion of our patients lived more than one year than those that Dr. Starzl reported, there has been a greater patient attrition at the 5- and 10-year period. With these small numbers, these variations from Dr. Starzl's series may not be significantly different, but I wonder whether there was any selective process, on the basis of tissue typing, in choosing his donor-recipient pairs.

We have never excluded any patients, and still don't, for tissue type, just for positive crossmatch.

Dr. John Sarkis Najarian (Minneapolis): Dr. Starzl stressed the durability of the transplant; and I think this is important. In our own experience, using our pediatric group as an example, of over 100 children during a ten-year period, we have found the same, or perhaps slightly better, degree of durability.

For instance, an actuarial table of our related kidneys in children reveals that we have 70% kidney survival at ten years, and practically no attrition between five and ten years. In our series of cadaveric kidney recipients 50% of the children are alive at ten years with functioning kidneys.

The remarkable thing is that 80% of the 100 children are still alive with first, second and third kidneys. None of the children are presently on dialysis. These data emphasize not only the durability of children, but also their ability to accept retransplantation so well.

Why are our results in children slightly better than those of an adult population? You will note from Dr. Starzl's slides that the parent group was his best group. The kidneys in our pediatric group were predominately from parent donors.

Another factor contributing to the poorer results in our adult recipient population is that deaths that occur in chronic patients are usually from causes other than immunologic causes. These non-immunologic causes of death, such as myocardial infarction, are becoming more and more of a factor as time progresses. In small children, however, this is not a problem.

I'm a bit perplexed by a couple of things, so I would like to ask two questions. First, in his typing data on the related donors his worst results were with the A-matched patients, those in which we would expect the best results. I wonder, when you look back on those patients, whether or not those patients were actually "overly immunosuppressed." In those early days we didn't really attempt to type them as we should have, and today if we transplant an A-matched patient, we reduce our immunosuppression, as I'm sure you do. If we had done so in the past perhaps we would have salvaged more patients.

If the same degree of immunosuppression is given to an A-matched patient as is given to a D- or E-matched patient, the patient is "over immunosuppressed", and can succumb to steroid problems and infections. I wonder if this is the way Dr. Starzl would look at that particular data.

The second question has to do with the glomerular lesion. It's intriguing to think about possible antigen-antibody viral glomerulonephritis, as Tom has mentioned. The lesion he showed was of membranoprolific disease. We have shown that in children and adults this disease has about a 50–60% recurrence, and is quite characteristic in pathology. I'm wondering if those that Dr. Starzl saw had membranoprolific nephritis as their original disease?

Dr. Thomas C. Moore (Torrance, California): When Dr. David Hume and I reviewed the Richmond transplant experience six years ago, we had the impression that a 2–3-year followup was needed to assess the results of the transplant effort. This appeared particularly true for the recipients of cadaveric donor kidneys. Approximately one-third of these recipients of cadaver donor kidneys in the Richmond experience at risk a minimum of three months had contracted hepatitis in the early posttransplant months, of which the majority died in liver failure between one and two years posttransplant.

In recent years my thoughts have changed somewhat concerning the period of major, if not exclusive, hazard to renal transplant function from the immune response to the transplant. I now feel that the great bulk, if not all, of the transplant damage from the host immune response in recipients who take their immunosuppressive medication as directed comes in the first year posttransplant.

When I visited Richmond four years ago to review the continuing function of transplants I had reported with Dave Hume, I was dismayed to find that three of the ten functioning related living donor transplants, at risk at minimum of six years—a group which corresponds to Dr. Starzl's current decade plus followup—that three of these ten, 30%, had been lost in the prior 12-month period, all to nontransplant failure causes. Two transplants were lost to rapidly fatal recipient malignant lymphomas, and one to recipient suicide. All three transplants had excellent function, with serum creatinines in the 0.8–1.1 range at the time of recipient death.

(Slide) We have recently studied the role of early transplant function classes F, F^{AR}, SF and NF, as shown on this slide, of Belzer machine preserved cadaveric kidneys on a long-term function, one to three years, of 146 kidneys transplanted at the USC County, UCLA Harbor, and UC Irvine transplant centers in our area.

One-year transplant survival was 51% for the F class, presumably nonpresensitized recipients; 29% for the F^{AR}, the accelerated rejection class; 65% for the SF, or the slow-functioning class; and 40% for the NF, or nonfunctioning class.

In the F functioning class, none of the five kidneys which survived for one year was lost after one year due to transplant rejection failure. There was one loss from death, a malignant perirectal lymphoma, at UC Irvine.

It is of particular interest to look at the non-F classes that may be presumed to be sensitized in varying degrees to donor antigens in terms of humoral antibody. In this particular group we find that the long-term function of cadaveric kidneys, which have experienced some degree of presumed immunological assault, is remarkably good for those transplants which recover from this early assault. For example, one year plus transplant survival of 88% for the F^{AR} group of kidneys; it is 79% for the SF group of kidneys; and it is 89% for the NF group of kidneys. The kidney in the presumably presensitized recipient which is not, in a sense, killed by early immunologic injury from humoral antibody and "primed" lymphocytes appears to acquire the privilege of long-term functional survival, possibly due to the development of enhancement.

The F-class transplants also offer a unique opportunity to study the effect of other factors in long-term function in presumably non-presensitized recipients. HL-A matching appears to play no significant role in long-term function.

Also for F recipients the use of splenectomy, carried out by Dr. Berne at USC County, appears to have a beneficial effect; 88% one-year survival of splenectomized recipients, as compared with only 44% for nonsplenectomized recipients, splenectomy having been carried out for either excessive transfusion requirements or for leukopenia.

I wish to ask Dr. Starzl three questions: 1) What per cent of the transplants lost after one year were due to rejection? 2) What was the role of early transplant function, if this data is available, in long-term survival of patients in his long-term series? And 3) what is your current feeling concerning the value of splenectomy clinically in the renal transplant patient?

Professor Maurice Rossie Ewing (Melbourne, Australia): At the Royal Melbourne Hospital we have a modest experience in renal transplantation, only recently having passed the 200 mark. Of these patients, all of them save two or three have been cadaver grafts. Only a handful of them, thus far, has passed the ten-year mark, so my remarks are not really relevant to the title of this paper; but we are, in fact, deeply disturbed already by the premature development, in the young, of the kind of degenerative changes in the skin with which we are very familiar in the elderly, after exposure over a lifetime to the sun. The incidence of skin cancer in the survivors after four years is 18%, and, of course, many of these patients have multiple skin cancers.

Thus far—I think, with only one exception—these skin cancers have been contained by simple surgical excision.

It's also a matter of interest that we have encountered a few patients, who have been put on long-term azothioprine for other causes, with skin cancer, but how these numbers relate to the total number at risk, and against a backdrop of a really high incidence of skin cancer in our community, it's not very easy to determine the relevance of this experience.

Professor Lars-Erik Gelin (Goteborg, Sweden): I rise to report the long-term results in our own series, (slide) which, however, only counts for the first eight years. And as seen, in the living donor series it's a 40% graft survival after eight years but only 18% cadaver grafts.

(Slide) This shows the patient survival for the same period of time, 65% in the living donor series and 40% in the cadaveric donor series.

(Slide) Our series is based on the principle that transplantation is the method of choice. We have no mortality in dialysis in our department. Everything goes on transplantation, and as soon as a graft is failing, we perform retransplantation and during a retransplant series we observed that in case we could do the retransplant while the prior, primary graft still had marginal function, the graft survival was very much superior to the situation when there is an interval between transplantectomy and regrafting, and this is the series showing this.

What is the mechanism behind this privileged time for retransplantation?

Dr. Thomas E. Starzl (Closing discussion): It seems to me that Professor Gelin's remarks illustrate the imperfections of treatment as it has been carried out in the last ten or 12 years, and, I would think, should be a real admonition not to consider this field fully developed.

It's my own conviction that some time in the next year or two there will be a very significant advance in immunosuppression, and possibly related to the kind of research work that is being carried out by Monaco and his associates in Boston, in which much more emphasis is being placed on the possibility of tolerance induction.

Professor Ewing's remarks could be used to make the same point as Professor Gelin's, because, obviously, the risk from the skin cancers—and we too have observed this—is clearly related to chronic immunosuppression. This matter may come up again in connection with Dr. Simmons' paper on the role of viruses in the oncogenetic mechanisms.

Naturally, I want to thank my old friend, John Najarian, and to try to answer his questions. Ours is a small series of A-matched sibling cases. We do believe there is an advantage of receiving an A-matched sibling kidney which did not, however, show up in our small early series but only later in our larger experience.

I don't think that over-immunosuppression led to the loss of those grafts that were still functioning in 1965, because we had already pulled off the heavy immunosuppression that we were using. By then, the patients were a year to two years posttransplantation, and by and large were in a pattern of light immunosuppression.

The question about the type of glomerulonephritis is an important and perceptive one. I tried to answer it in the manuscript, but it would take too long, and I'm not expert enough in pathology to warrant going into it at this time.

Dr. Wilson, you asked two questions. One concerned the type of selection. Like you, our selection was fortuitous in those years, 1962 to 1964, since there were no good or even acceptable donor-recipient typing techniques at that time. In fact, we did not even bother to follow the rules of red blood type matching, which have become recognized to be of such paramount importance since then. Thus, good matching was not a factor.

Dr. Wilson, with his customary modesty, focused only on this period of time that I did, and failed to mention that the longest homotransplant survival in the world is a Boston recipient of a fraternal twin kidney treated in 1958. As I understand it, that patient is still alive.

Dr. Belzer raised the question about whether kidneys can be permanently accepted in the human being, as they can in animals. In our manuscript we relate an experience with two patients who stopped their immunosuppression—probably, in one case, in 1971. The second patient definitely stopped his immunosuppression about 15 months ago. Neither recipient has suffered any ill effects. But we certainly have our fingers crossed, because the story that Dr. Belzer has told has been repeated now on many occasions, and usually with dire consequences.

Dr. Moore asked three specific questions. One concerned our opinions about the stability of grafts after one year, and we agree with him, in general, that as the life survival curves would indicate, there is relative stability. Second, we believe the greatest risk the transplant recipient must face is not cancer or infection, but slow failure of his homograft with physical deterioration before retransplantation or return to dialysis.

The question about early function versus late results is one I cannot answer on the basis of these data, because, as you may remember, almost all of these kidneys functioned superbly from the beginning. Therefore, it would be difficult to make the kind of correlations that you suggest.

Splenectomy, as far as I'm concerned, is an unproven issue in the human, and probably is not provable on the basis of clinical investigation. If you believe in basic biology, there is plenty of evidence that splenectomy is a biologic immunosuppressive maneuver, but just what effect it has on transplant survival, I think is unanalyzable.

May I make one final comment before closing? This is the first American Surgical meeting that I have ever been to that was not graced by the presence of Dave Hume. It is strange to give a paper on Dave's favorite subject, realizing that his smiling face and swashbuckling emanations are not today, or ever again, going to be working their way to the podium—usually down that aisle (indicating)—to set up a lively but always good-natured duel.

I, for one, have no intention of forgetting our good friend simply because he is not with us today. Thank you.

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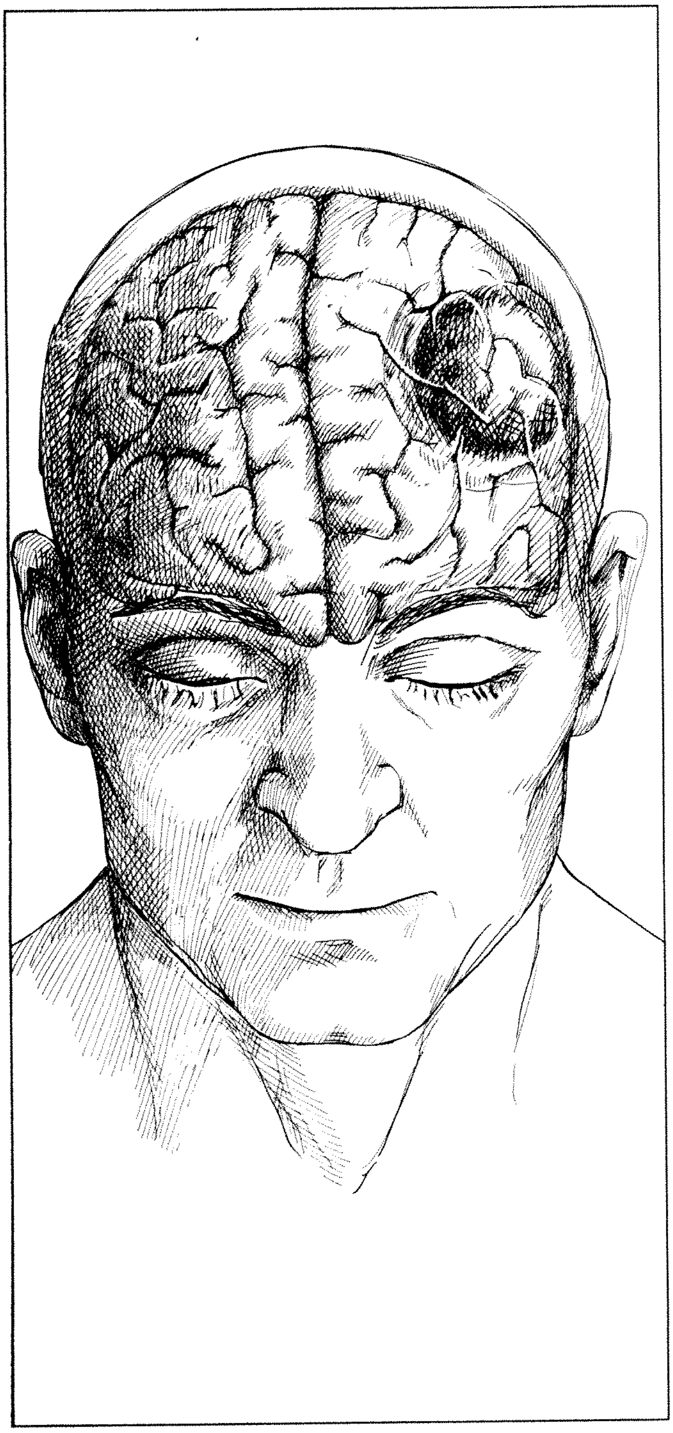
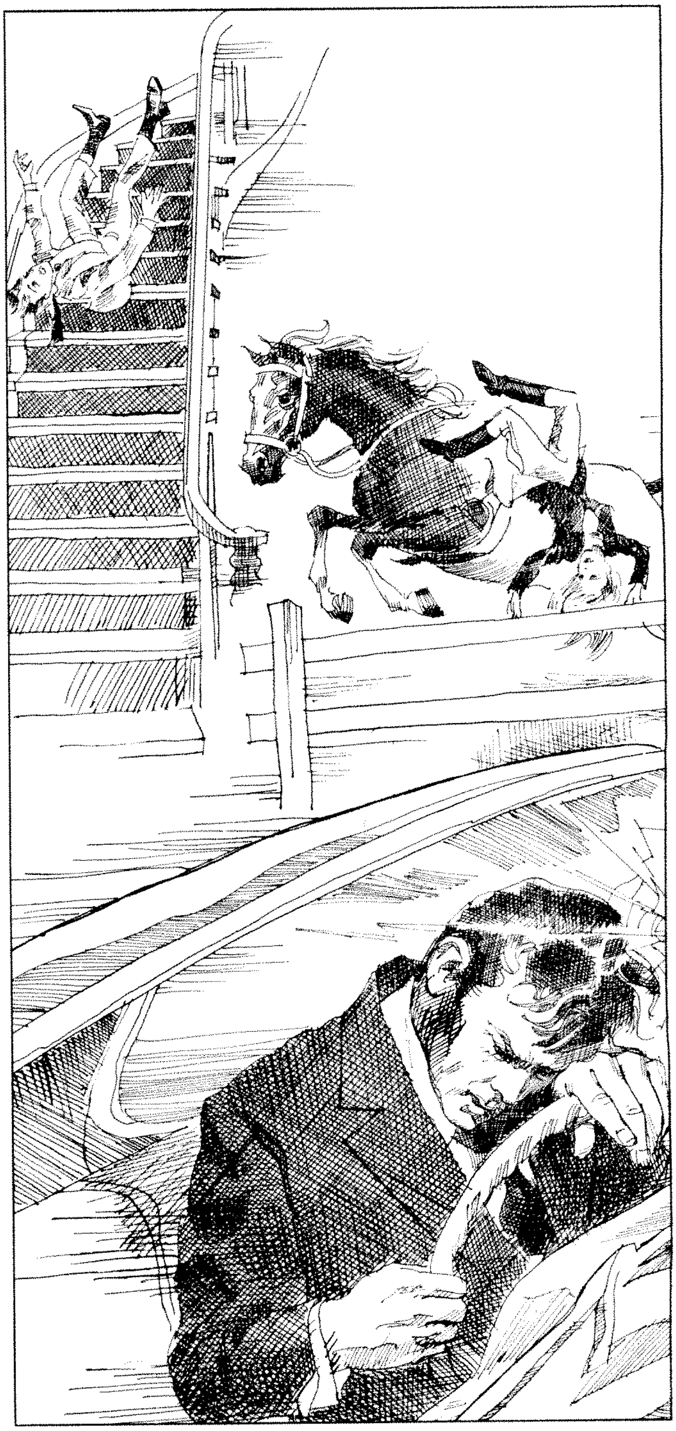
cerebral

expect it as a possible complication of primary or metastatic brain tumor.

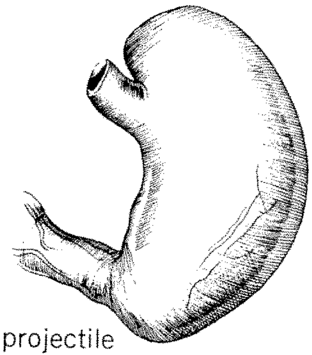


expect it in the presence of severe head injury.

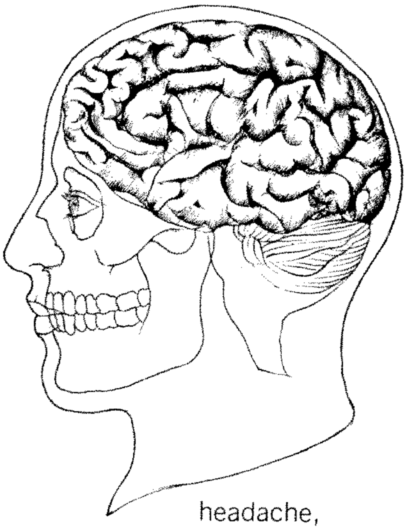


edema*

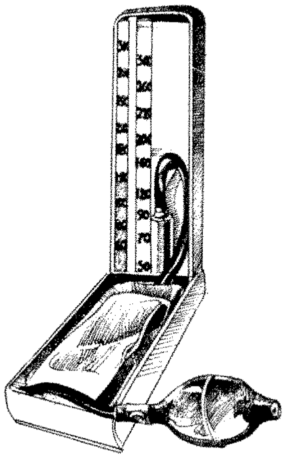
suspect it in the presence of signs and symptoms such as these:



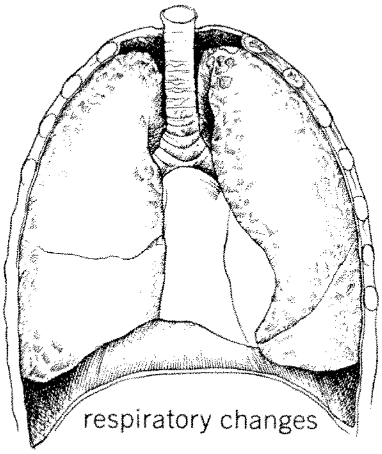
projectile vomiting



headache, altered consciousness

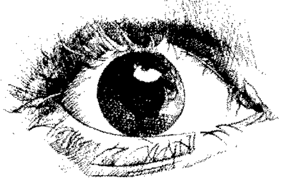


increased blood pressure

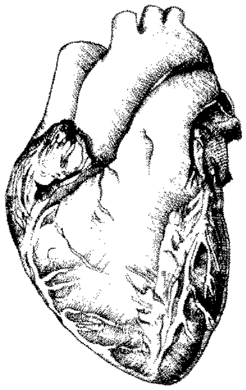


respiratory changes

dilated pupil, papilledema,



unilateral or bilateral abducens palsy



bradycardia

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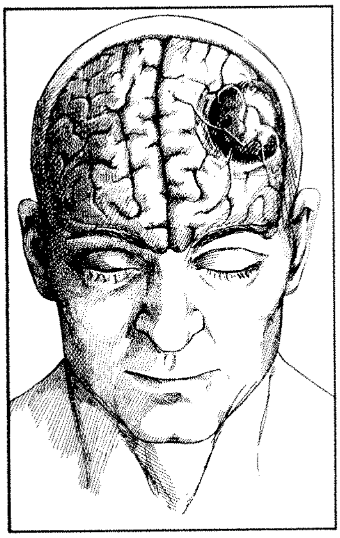

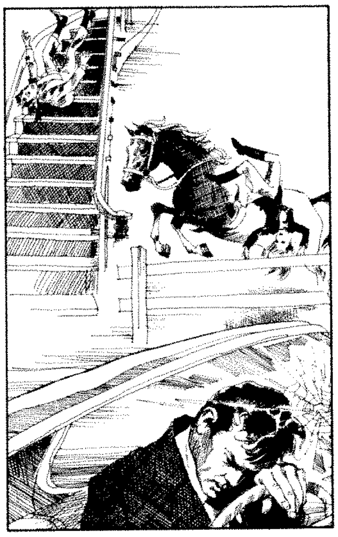

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Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

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Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

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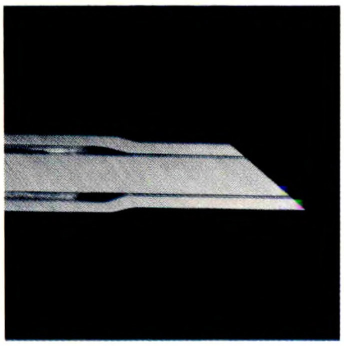

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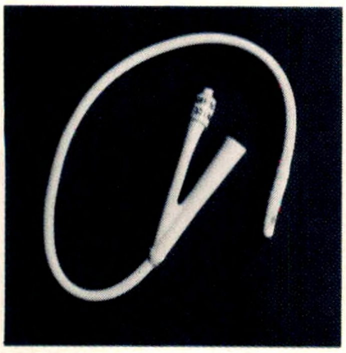

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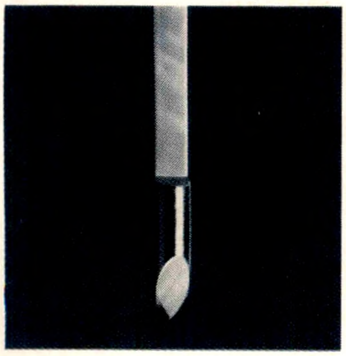

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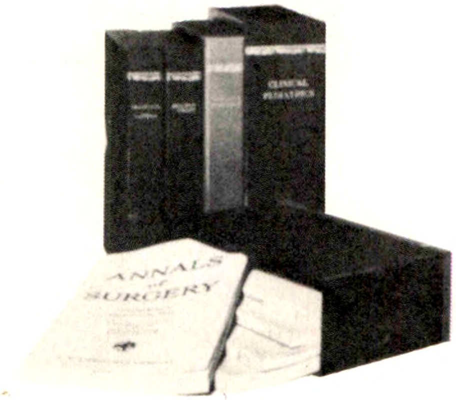

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Thiamine HCl (B_1)	50 m
Riboflavin (B_2)[11]	10 m
Pyridoxine HCl (B_6)	15 m
Niacinamide	100 m
Dexpanthenol	25 m
Vitamin E* (dl-alpha tocopheryl acetate)	5 Int. Uni

[1] With sorethytan laurate 1%, sodium hydroxide 1%; and ge tisic acid ethanolamide 2% as preservative.

[11] With propylene glycol 30% as stabilizer and preservativ sodium hydroxide for pH adjustment, and sorethytan laura 1.6%; in Concentrate as riboflavin-5-phosphate.

*Oil-soluble vitamins A, D and E water solubilized wi sorethytan laurate; covered by U.S. Patent No. 2,417,299.

BRIEF SUMMARY

INDICATIONS: *in emergency feedings*—Surgery, exte sive burns, fractures and other trauma, severe infectio diseases, comatose states, etc. may provoke a "stress" s uation with profound alterations in the body's metabo demands and consequent tissue depletion of nutrients. As result, wound healing may be impaired, enzyme activity di turbed, hematopoietic tissues affected; hypoproteinem and edema may appear; convalescence is thus prolonged. In such patients M.V.I. (administered in intravenous flui under proper dilution) contributes optimum vitamin intak toward maintaining the body's normal resistance and repa processes.

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For intravenous feeding, one daily dose of 10 cc. of M.V.I. 5 cc. of M.V.I. Concentrate added directly to not less tha 500 cc., preferably 1,000 cc., of intravenous dextrose, salir or similar infusion solutions...plasma, protein hydrolysate etc.

PRECAUTION: Allergic reaction has been known to occ following intravenous administration of solutions containir thiamine.

CAUTION: Not to be given as a direct undiluted intraveno injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be disco tinued as early as practical in favor of an intramuscular oral vitamin preparation, if deemed advisable.

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◀ See opposite page for product Brief Summary.

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*M.V.I. formula contains vitamins B_1, B_2, niacinamide, dexpanthenol and B_6. If needed, vitamin K, vitamin B_{12} and folic acid may be optional additions to parenteral nutrition programs utilizing M.V.I.

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MEDI-SCAN Q&A

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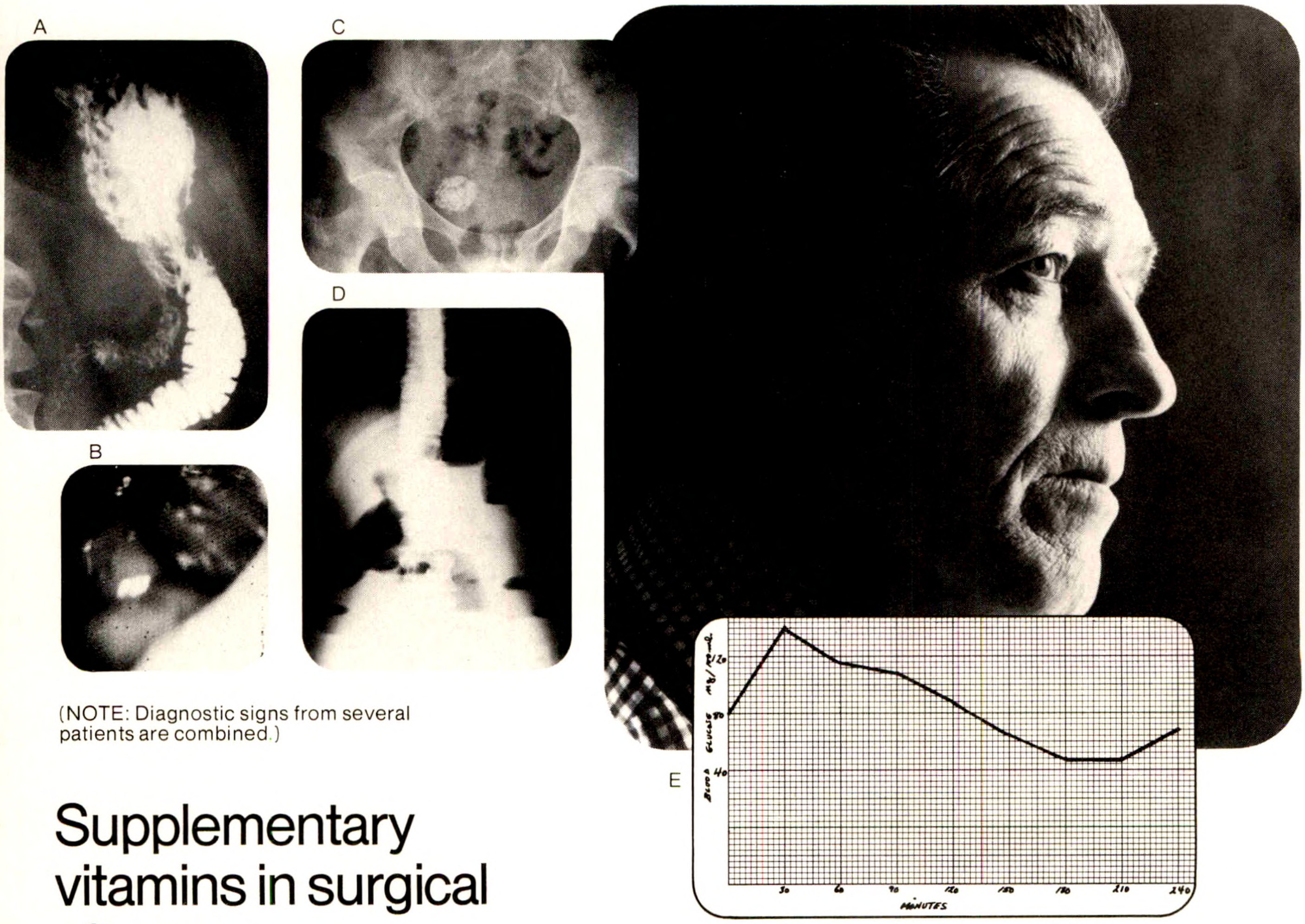

(NOTE: Diagnostic signs from several patients are combined.)

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**Diagnosis appears on next page.*

See next page for summary of Product Information.

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#100
Sig: 1 Tab
B.I.D.

DIAGNOSIS: Postgastrectomy (Billroth No. II) and its complications: (A) Barium meal showing gastrojejunostomy; (B) Endoscopy showing gastrojejunostomy; (C) X-ray of the pelvis showing osteoporosis; (D) Flat plate of the abdomen showing small bowel obstruction; (E) Glucose tolerance test showing late hypoglycemia.

Please see complete product information, a summary of which follows:

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Thiamine mononitrate (Vitamin B_1)	15 mg
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Niacinamide	100 mg
Calcium pantothenate	20 mg
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Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

Dosage: 1 or 2 tablets daily, as indicated by clinical need.

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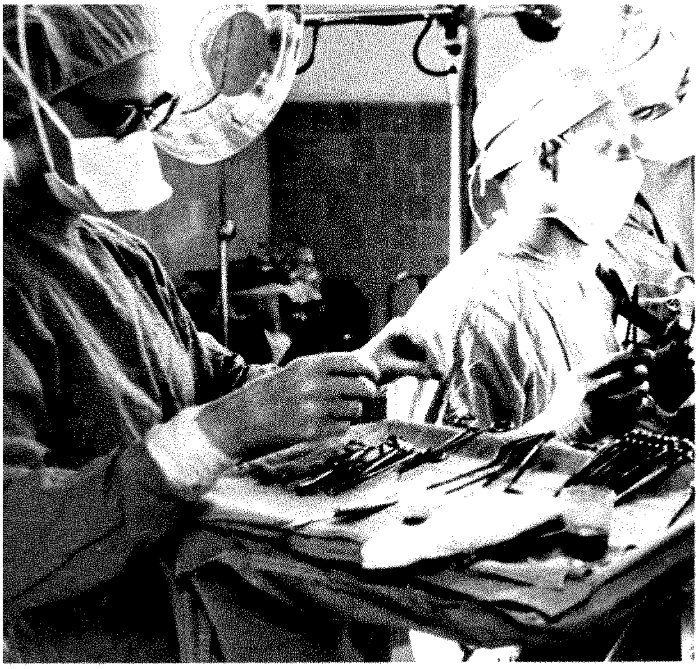

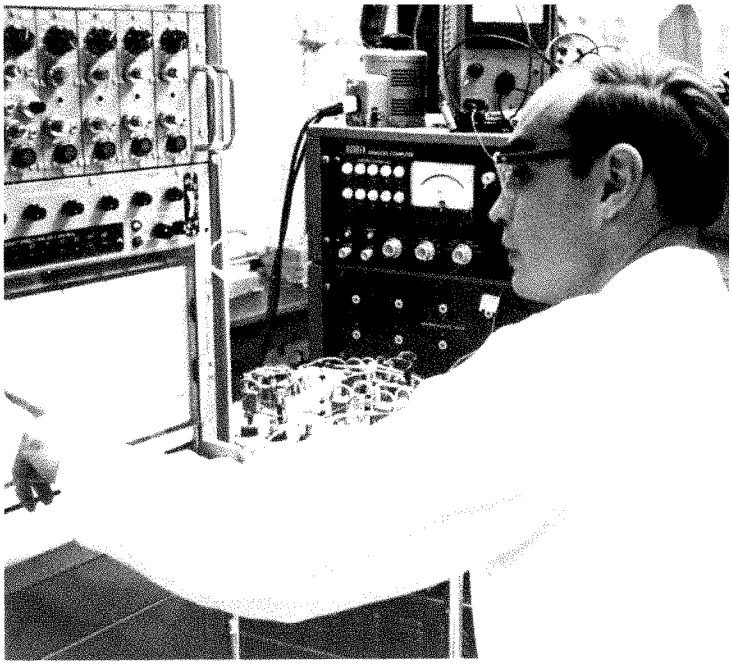

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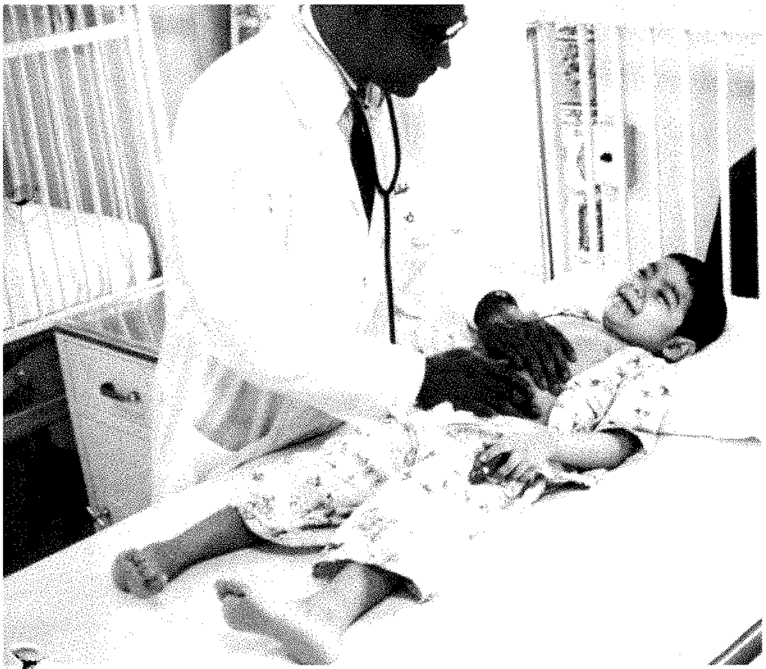

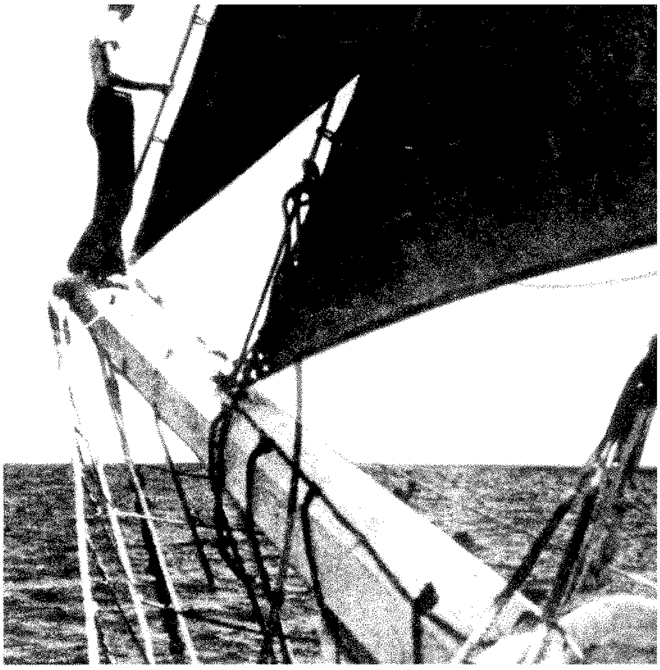

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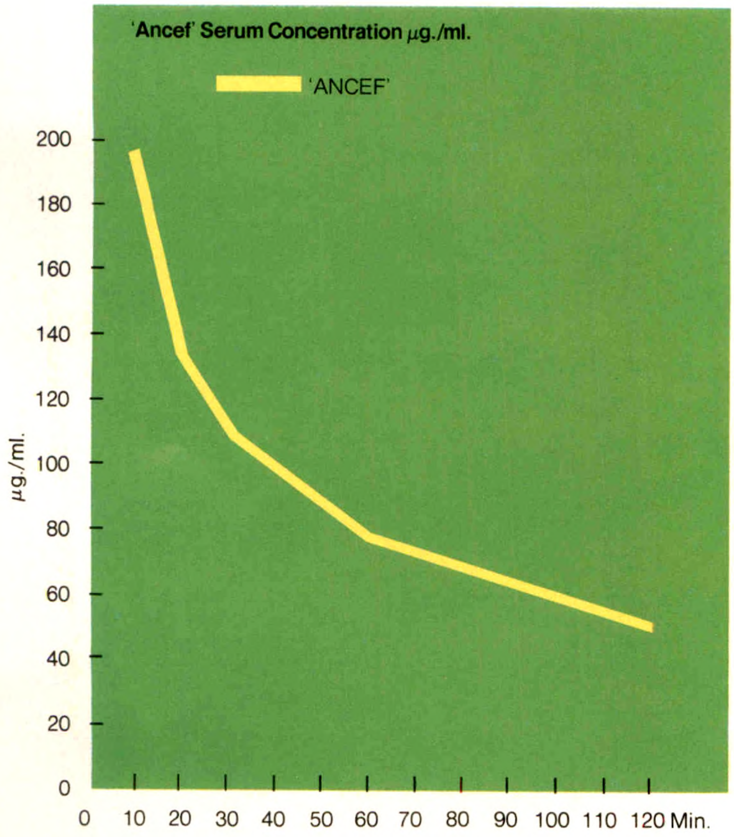

Average Serum Concentration of 'Ancef' following a single 1 gram I.V. injection. (Study conducted in 20 healthy adult volunteers.)

'ANCEF' Indications

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, S. aureus* and group A beta-hemolytic streptococci.

Genitourinary tract infections due to *E. coli, P. mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *S. aureus*, group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *S. aureus*.

Septicemia due to *D. pneumoniae, S. aureus, P. mirabilis, E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

'ANCEF' I.V. has a low risk of phlebitis at the injection site.

Duration of I.V. Therapy	Number of Patients	Average Daily Dose	Number with Phlebitis
1 day or less	13	3.0 g.	1
2 days	43	2.6 g.	1
3 days	31	3.3 g.	1
4 days	19	2.6 g.	1
5 days	37	2.6 g.	1
6 days	26	4.7 g.	0
7 days	26	3.8 g.	0
8 days	17	3.0 g.	0
9 days	11	3.1 g.	0
10 days	6	2.7 g.	0
More than 10 days	44	4.9 g.	1
Total	273	3.4 g.	6 (2.2%)

Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. As can be seen in the above chart, which presents the duration of I.V. therapy, average daily dose and the occurrence of phlebitis, most cases of phlebitis occurred in the first few days of therapy which may be indicative that the inflammation was caused by the mechanical trauma of setting up the I.V. rather than continuing irritation of the drug itself.
These data were derived from pre-marketing clinical studies in small populations. Further clinical experience may reveal a greater incidence of adverse effects.

Pain on injection is infrequent with 'Ancef'.

ANCEF® Has Produced No Nephrotoxicity in Extensive Clinical Trials.

(Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.)

Adverse Reactions.

Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy, please see brief summary of prescribing information on next page.

See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.

Smith Kline & French Laboratories
Division of SmithKline Corp., Phila., Pa. 19101

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

(lyophilized)

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro*:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae	*Klebsiella* species
Escherichia coli	*Enterobacter aerogenes*
Proteus mirabilis	*Hemophilus influenzae*

Most strains of *Enterobacter cloacae* and indole positive Proteus *(P. vulgaris, P. morgani, P. rettgeri)* are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus*.

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef' every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories, Division of SmithKline Corp.,
Philadelphia, Pa. 19101

Correlation Between MLC Stimulation and Graft Survival in Living Related and Cadaver Transplants

KENT C. COCHRUM, D.V.M., OSCAR SALVATIERRA, M.D.,
FOLKERT O. BELZER, M.D.

From the Transplant Service, Department of Surgery, University of California, San Francisco, California

"Multiple MLC's" (parallel tests in recipient, donor and globulin-poor plasma) were performed in 211 consecutive transplant donor-recipient pairs. The two-way MLC's were performed on patients' lymphocytes before immunosuppression. All grafts regarded as "successful" were at risk for at least six months. Patients with a low MLC (Stimulation Index less than 8 times controls) usually had successful grafts (graft survival was 83% in related transplants and 76% in cadaver transplants). Patients with high MLC's had poor graft survival (0% graft survival in related transplants and 32% in cadaver transplants). An adjusted graft survival was calculated to exclude patients who died with normal renal function (serum creatinine less than 2 mg%). The adjusted graft survival was 91% for living related transplants and 88% for cadaver transplants. Falsely low MLC's occurred when the recipient's plasma contained low-titer cytotoxic antibodies. In 15 recipients of cadaver kidneys, the MLC in recipient plasma was significantly lower than MLC's in donor or globulin-poor plasma. Since the MLC when using cadaver donors was necessarily retrospective, the results were not known pre-transplant and all 15 grafts were rejected. In living related pairs, however, we were able to screen for such antibody activity and could avoid humoral presensitization and cellular compatibility.

THE MOST RECENT REPORT of the Kidney Transplant Registry shows graft survival at one year to be 74% when sibling donors are used, and 76% when parental donors are used. Although this appears to be a significant improvement over the 50% survival obtained with cadaver organs, it still means that one of four living related grafts fails within the first year. Obviously, there is a great need for improved, pre-transplant matching of donor-recipient pairs. At present, there are two techniques used for such matching: HLA tissue typing and the mixed lymphocyte culture test, or MLC. Although HLA typing has proved of great value in identifying HLA identical siblings, it has not been useful in selecting between less well-matched related donors such as parents and siblings who share one haplotype or less with the recipient. Because the Mendelian odds for HLA identity are not very high and because non-HLA factors are strongly indicated by most graft survival data, interest in mixed lymphocyte culture testing is increasing.

The data presented here will summarize the results of preoperative MLC/s performed on 212 consecutive transplants at the University of California School of Medicine, San Francisco (i.e. 59 living related pairs and 153 unrelated pairs). This group includes patients who could be considered "poor risks," i.e. patients receiving secondary grafts; small children; diabetics; patients with lupus erythematosis; etc. A graft must have been at risk for at least six months to be represented as "successful" in our data. Graft loss on the other hand, includes not only graft rejection but death of the patient from any cause. All MLC tests were performed pre-transplant; however, when cadaver organs were used, the results were available only after transplantation because of the five-day incubation period needed to perform the MLC and the present limitations of organ preservation.

Methods

Sixty milliliters of heparinized blood were obtained from the donor and the recipient before transplantation and before any immunosuppressive drugs were administered to the recipient. The blood was then separated

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Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

Supported by USPHS Clinical Grant No. AM-11290 and USPHS Grant No. AM-1567.

on a Ficoll/Hypaque density gradient to obtain a purified lymphocyte population (90–95% mononuclear cells contaminated by less then 5% erythrocytes and granulocytes). Platelets were removed during the subsequent rinsing of the lymphocytes (three times in balanced salts). The purified and washed lymphocytes were cultured in two-way MLC's which consist of 5-replicate mixtures and triplicates of each of the appropriate controls. Mixtures contained 1×10^6 donor lymphocytes plus 1×10^6 recipient lymphocytes in 4 ml of medium. Control cultures contained 2×10^6 donor or recipient lymphocytes, again in 4 ml of medium. The medium used was tris-buffered Eagles' MEM-S with antibiotics and L-glutamine.[8] Parallel MLC tests were cultured in 10% recipient plasma, 10% donor or AB plasma and 10% plasmanate. This battery of tests is called the "multiple MLC." After 5 days in culture the cells were labeled with tritiated thymidine (5 microcuries per 4 ml. of culture; 6.7 curies per m mole) for 3 hours. The acid insoluble DNA fraction was precipitated and collected on filters which were then burned on a Packard tricarb oxidizer for liquid scintillation counting. The counts of replicate cultures were averaged and expressed as counts per minute per culture. The degree of stimulation in each test is expressed as a ratio between the counts of the mixture and those of the appropriate controls; this is the Stimulation Index or SI.

$$\text{SI} = \frac{\text{Counts Per Minute Mixture } (A + B)}{\text{CPM of A control} + \text{CPM of B control} \div 2}$$

The counts per minute of the replicate cultures seldom varied more than 10% from one another.

Results

The results of the MLC in 59 related transplants are given in Table 1. We have divided the patients into two groups: Those with a SI lower than 8 and those with a SI of 8 or above. The MLC data in this and other tables refer to MLCs done in recipient plasma. Fifty-six recipients of living related grafts had low MLCs with their donor (i.e., SI of less than 8). Of these grafts, 47 (83%) are functioning normally at present (from 6 months to 3 years post-transplant). Five patients died with functioning kidneys. Only one of these patients had an elevated serum creatinine (2.4 mg/100 ml) at the time of death. If the 4 patients who died with "normal" serum creatinines (i.e., less than 2 mg/100 ml) are not considered graft losses, graft survival would be 91% or the adjusted graft survival.

TABLE 1. *Correlation of MLC Results and Graft Survival in Related Transplants*

MLC SI*	Number of Patients	Graft Survival	Adjusted Graft Survival
<8	56	83%	91%
>8	3	0%	0%
	Two-Year Graft Survival		
<8	31	80%	92%

* Stimulation Index in 10% recipeint plasma.

TABLE 2. *Correlation of MLC Results and Graft Survival in Cadaver Transplants*

MLC SI*	Number of Patients	Graft Survival	Adjusted Graft Survival
<8	85	76%	88%
(False Neg)	15	0%	0%
>8	53	32%	33%
	Two Year Graft Survival		
<8	28	71%	87%
>8	21	23%	23%

* Stimulation Index in 10% recipient plasma.
(False Neg) = False negative MLC

Only three patients who had high MLCs with their related donors received transplants. All of these grafts were rejected.

The two-year graft survival for patients with low MLCs is 80% (i.e., 24 out of 30 patients have normally functioning grafts). The adjusted graft survival for this group is 92%.

The correlation between our MLC results and graft survival in 15 patients who received cadaver organs is shown in Table 2. Eighty-five patients had SIs of less than 8. Sixty-five of these patients (76%) still have functioning kidneys and seven have rejected their kidneys. Thirteen patients died, but only 4 of the 13 had elevated serum creatinines, or had been treated for rejection within 6 months prior to death. If the 9 patients who died with normal kidney function are not considered graft losses, the adjusted graft survival is 87% for cadaver recipients with low MLCs. Fifteen recipients of cadaver grafts had falsely low MLCs in their own plasma. This was detectable only by an analysis of the multiple MLC. These falsely low MLCs occurred when the recipient's plasma contained humoral cytotoxic antibodies against the donor. All 15 patients had very low MLCs (SI less than 1.8) in their own plasmas. However, the parallel MLCs in 10% donor plasma and 10% plasmanate were significantly higher. Since MLC tests are retrospective when cadaver organs are used due to the 5-day incubation period, these results were known only post-transplant and all 15 grafts were rejected. All 15 recipients had had negative pre-transplant cytotoxic cross-matches with their respective donors' cells. However, the recipients did develop cytotoxic antibodies after their rejected kidneys were removed.

Fifty-three recipients of cadaver kidneys had high MLCs and only 17, or 32%, of these patients now have functioning grafts. One patient died from myocardial infarction one month post-transplant. This patient had a serum creatiine of 1.3 at the time of death. If this patient is not considered a graft loss, the adjusted graft survival in patients who had high MLCs with their cadaver donors is 33%.

The two-year graft survival for the cadaver recipients with low MLCs was 71%. Twenty of the 28 patients in this category have serum creatinines of less than 2 mg/100 ml. The adjusted graft survival for this group was 87%. Only 5 of the 21 patients with high MLCs have functioning grafts at two years post-transplant.

Discussion

The survival of allogeneic grafts depends upon the degree of genetic disparity between donor and recipient. At present, there are two methods of selecting human donor-recipient pairs: 1) serological HLA phenotyping; and 2) matching by mixed lymphocyte cultures tests (MLC). Many studies have been published on the correlation between matching for HLA antigens and renal allograft survival. There is general agreement that a graft from a HLA identical sibling has a 90% chance or better for long-term survival, in contrast to the significantly lower survival rate of mismatched sibling grafts. However, when unrelated donors are used, a good correlation between HLA matching and graft survival has not been demonstrated.[6,11] This would indicate a major participation by non-HLA factors in graft rejection. Since the description of the mixed lymphocyte culture reaction (MLC) by Bain,[5] several investigators have tried to demonstrate a relationship between this phenomenon and histocompatibility.[1,3] Studies by Bach and Amos[2] initially showed that MLC reaction between siblings corresponded to the HLA match between them. However, the same investigators later found an HLA identical sibling pair that stimulated in MLC.[1] Studies by Yunis and Amos,[16] and by Eijsvoogel *et al.*,[9] have shown that the MLC reaction is an expression of disparity at a genetic locus which is distinct from, but closely linked to, the serologically defined HLA locus.

The MLC test was first suggested as a method for the pre-transplant selection of donor-recipient pairs by Bain in 1965[5] and by Bach and Amos[2] in 1967. Early reports on the correlation between the degree of stimulation in MLC and the length of skin graft survival were made by Ceppellini *et al.*,[7] and Russell *et al.*[14] Bach[4] and Hamburger[12] later demonstrated a correlation between a positive or negative reaction in the two-way MLC and the clinical results of their living related renal transplants.

We have previously reported a correlation between the results of our two-way MLCs and graft survival in our living related transplants.[8] In contrast to most investigators, we have continued to use the two-way test in which both donor and recipient cells are potentially able to participate. This is because we and others[4,12] have found that tests rendered one-way by treatment of the donor cells with either Mitomycin C or X-irradiation have not correlated as well with actual graft prognosis. Although it could be argued that a two-way MLC could just as well reflect the perhaps irrelevant response of donor to recipient, this would not interfere with the identification of low reactors.[10] In fact, we have demonstrated that the MLC can show some response and still be predictive of good graft survival. However, if the MLC reacted over a certain degree (i.e., SI over 8), graft survival was poor.

For the first time we were able to demonstrate a positive correlation between MLC results and graft survival in cadaver transplants. This was later confirmed by Kashiwagi *et al.*[13] In addition, Van Rood[15] has also demonstrated a significant correlation between MLC results and skin graft survival in unrelated donor-recipient pairs.

The data presented here give further support to the important role of MLC matching in renal transplantation. The 56 related donor-recipient pairs with low MLCs had an overall 83% graft survival and a two-year graft survival of 80%. This is to be compared with the 67% to 69% survival for grafts between living related pairs reported by the Transplant Registry. The three living related pairs with high MLCs who were transplanted had poor graft survival.

The MLC results were also predictive of unrelated graft survival. The cadaver recipients with low MLCs had an overall graft survival of 76% and a two-year graft survival of 71%. These results are a considerable improvement over the 46% two-year graft survival reported by the Registry. Cadaver recipients who had high MLCs with their donors had a graft survival rate of only 32%, which decreased to 23% at two years.

We have previously reported on the use of the multiple MLC (i.e., parallel MLCs in recipient, donor, and globulin-poor plasma) to detect presensitized patients.[8] We have now identified 15 cadaver recipients who were presensitized and also had false-negative MLCs. These patients all had secondary grafts and had had very low values when the MLC was done in their own plasma, but had higher values when the same MLC was done in donor plasma or a non-specific protein source. This rise in MLC value was particularly impressive when

TABLE 3. *Cause of Death After Transplantation in Patients With a Low MLC*

	Cause of Death	No. of Patients
1. Patients dying with normal renal function. (Serum Creatinine < 2; mean value 1.4)	Myocardial Infarction	2
	Suicide	1
	Pulmonary Emboli	2
	Non Bacterial Infection	
	Viral Encephalitis	1
	Cytomegalovirus	1
	Pneumocystis	1
	Toxoplasmosis	1
	Bacterial Infection	1
	Hepatitis	1
	G. I. Bleeding	1
	Hyperparathyroid Crisis	1
		13
2. Patients dying with Serum Creatinine > 2 or recently treated for rejection.	Non Bacterial Infection	
	Cytomegalovirus	1
	Pneumocystis	2
	Bacterial	1
	Fungal	
	Nocardia	1
		5

it occurred in 10% plasmanate. Since plasmanate is virtually free of gamma globulin, it loses a good deal of its supportive value for the metabolism of the MLC, and tests on it are usually quite low. However, if the patient has alloantibodies, and therefore a falsely low MLC in his own plasma, the concomitant test done in plasmanate gives a higher value. Thus, the inhibitory effect of recipient plasma with antibodies against the donor can be so great that even a medium which gives less than optimum support can yield higher stimulation. The importance of detecting circulating antibodies by this method can not be over emphasized since all of these patients rejected their kidneys.

Since prolonged immunosuppression can have profound psychological and/or physiological effects, we feel that the death of any transplant recipient could be transplant-related. However, when a patient dies with a perfectly functioning kidney, it is difficult to regard it as an immunological graft loss. We therefore have calculated an "adjusted graft survival" to separate graft loss due to immunological causes from graft loss due to the patient's death. The adjusted graft survival data have been calculated for both living related and cadaver recipients. We have divided the patient deaths into two groups (Table 3). Group 1 includes those patients who had a stable serum creatinine value of less than 2 mg/100 ml for at least 6 months prior to death. These patients were on maintenance immunosuppressive therapy and had not been treated for rejection within the 6 months prior to death. Group 2 included patients with elevated serum creatinine values, and patients who died with a normal creatinine but who had been treated for rejection within 6 months preceding death. If the patients dying with normal renal function (Group 1) are not considered graft losses, we obtained an "adjusted graft survival" value for living related recipients who had low MLCs with their donors. This was more than 90% even at two years. Similarly adjusted data give a two year graft survival of 87% for unrelated transplants with low MLCs.

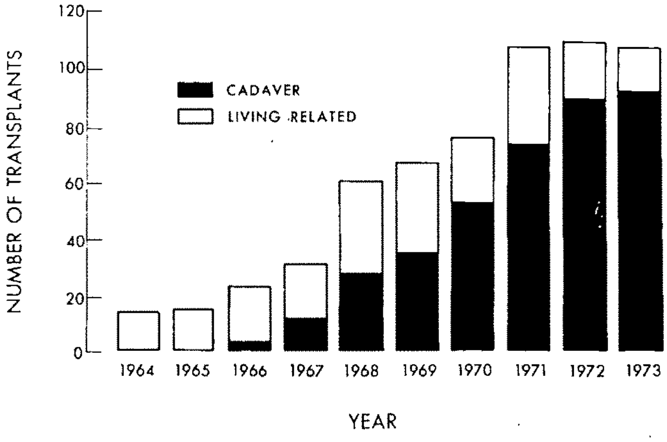

FIG. 1. Renal transplants by year and donor source.

In September of 1972 we made it our policy to transplant only those living related donor-recipient pairs who had consistently low MLCs. Recipients having demonstrably false negative MLCs, or consistently high MLCs were placed in the computerized recipient pool to await a cadaver organ. Patients receiving related transplants under this policy have had a graft survival rate of 88% for up to 1½ years post-transplantation. In an attempt to provide kidneys for those recipients denied related transplants by this policy, we have had to rely on our already active organ procurement program.

Figure 1 illustrates the total number of renal transplants performed at the University of California School of Medicine at San Francisco over the past 10 years. Because large numbers of cadaver organs are available we have been able to give kidneys to 8 of the 9 patients referred to the cadaver program because of their poor MLC results.

In an effort to make cadaver transplantation as safe as possible we have adopted a more conservative immunosuppressive program for our transplant recipients. Using this new regimen, we have been able to increase patient survival from 85% to 93% for the recipients of cadaver organs and from 91% to 100% for the recipients of related kidneys.

Since HLA identity in a random population is so unlikely, HLA matching for the use of cadaver organs is not only inadequate but also impractical. The first because it has not been shown to correlate well with clinical graft survival; the second because it necessitates such a large recipient pool to achieve good antigenic matches. A reliable pre-operative MLC for the recipients of cadaver kidneys would enable the use of a significantly smaller recipient pool. The test could be used as a sort of "cellular cross-match" in which a pool recipient could be tested against every available donor with an appropriate blood type and a negative cytotoxic cross-match. Our data already indicate that almost 50% of our recipients have acceptable MLC reactions with their donors.

We are very encouraged by our success in using the MLC as a screening device for related transplants. It now remains to adapt the test so that it can be used pre-operatively for the recipients of cadaver organs, or to improve organ preservation so that enough time is available to perform the present MLC.

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DISCUSSION

DR. JOHN SARKIS NAJARIAN (Minneapolis): Unfortunately, as Dr. Cochrum has pointed out, the studies with MLC in the cadaver donors were done retrospectively, since the tests takes five to seven days to perform; it showed significance. Therefore, there is an urgent need for a MLC test that can be performed in 24 to 48 hours. The aspect I'm interested in, however, is the related donor side of transplantation. Cochrum and Belzer report three patients with related donors, who had high MLCs before transplansplant. All three transplants failed. Apparently, since that time, or since 1972, they have not done related donor transplants with a high MLC. That's three out of some 57, so it's less than 6%.

Dr. Cochrum, how often have you seen a high MLC in a related donor since 1972? Is it still running about 5 or 6%, or is the figure higher?

In addition, you didn't mention HL-A, and I am curious to know what the HL-A typing of the three failures were. Were they really bad matches by HL-A, or were they reasonably good matches?

The overall result in the cadaveric group, as I read it, was around 54 to 58%, 1- and 2-year survival, which is quite consistent with the national survival. So if you could get rid of that 33% survival group, you would really do very well. Maybe Dr. Cochrum can tell us if you have been able to find a rapid MLC that most of us can use to help us select these patients.

DR. G. MELVILLE WILLIAMS (Baltimore): I'd like to ask two questions. The first question has to do with the bad results obtained by the current investigators when preoperative serum was found to block the mixed lymphocyte reaction between donor and recipient. It had been my impression from previous reports by these and other investigators that the MLC blocking in the absence of cytotoxic antibody to the donor frequently led to good results rather than disasterous results. I wonder if the authors could clarify the discrepancies between this report and previous ones.

The second question has to do with the whole concept of what the MLC reaction measures. I have been struck in our small experience with delayed hypersensitivity testing of patients waiting for cadaveric transplantation that there exists a correlation between an ability to respond to dinitrochlorobenzene and rejection. Individuals that are anergic to dinitrochlorobenbene have a much better course following transplantation.

Could it be that the MLC is simply measuring inherent responsiveness or lack of responsiveness on the part of the recipient's lymphocytes? I think the key question here is: do you find an enormous spread in responsiveness generally, so that some recipients are highly stimulated by any type of cell whereas others do not respond to any cells? That is, are low responders in culture consistently so or is there a spectrum of response depending upon the origin of the stimulating cell.

DR. KENT C. COCHRUM (Closing discussion): To answer Dr. Najarian, we find that approximately 15% of our living related donor-recipient pairs that we match either have a high MLC or are presensitized against the prospective donor.

We are finding more and more patients that are of the presensitized type, and we are having to turn down more and more patients because of this. These are the patients that do fairly well for two or three days, and then have a fairly progressive rejection over a short period of time.

All of the living related donor-recipient pairs that we showed except seven were one-haplotype matches. The three with high MLCs were one-haplotype matches. Two of the three shared three antigens with the donor.

Dr. Williams, we have found the case to be that when recipient serum is used, 99% of the time, if there is an inhibitory factor pretransplant, this is cytotoxic in nature. We have only found one patient in whom we felt pretransplant that the patient could be classified as having an enhancing type of antibody. We were very excited by these inhibitory factors that we found at first, but as the rejections began to pile up it became very evident that we were detecting presensitized patients.

Cytomegalovirus:

Clinical Virological Correlations in Renal Transplant Recipients

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One-hundred thirty-two renal transplant recipients were systematically screened for viral infections and the findings correlated with the clinical course. One-hundred ten patients showed evidence of infection with herpesviruses and 89 patients showed laboratory evidence of infection with cytomegalovirus (CMV) uncomplicated by bacterial infections or technical complications. Patients without viral infections were usually asymptomatic. After recovery and development of anti-viral antibodies, most patients were asymptomatic despite the persistence of viral excretion in the urine. In contrast, the onset of viral infections were almost always accompanied by a significant clinical illness characterized by fever, leukopenia, and renal malfunction. Of 89 patients with cytomegalovirus infections, 83 survived at least three months. In these patients, the fever appeared to be self-limited and resolution of the fever was accompanied by increases in anti-CMV antibody. Renal biopsies demonstrated typical rejection reactions in all the biopsied patients and renal malfunction usually responded to anti-rejection treatment. Six of the 89 patients with CMV infections died within a month of viral isolation. These patients could be distinguished from those who recovered by a decreased or absent antibody response to the virus, suppressed lymphocyte responses to mitogen in autochthonous blood, and absent histologic evidence of rejection in the renal allografts. Thus, two paradoxical responses to CMV infections are seen in transplant patients: In the relatively immunocompetent patient, the infection is associated with renal allograft rejection, a prompt antibody response to the virus, and recovery. The severely immunosuppressed patient cannot make an antibody response, does not exhibit allograft rejection as a cause of renal malfunction, he may be further immunosuppressed by the viral infection, and is susceptible to sequential opportunistic infections leading to death.

HILL *et al.*,[17] and Hedley-Whyte and Craighead,[16] were the first to implicate cytomegalovirus (CMV) in the pathogenesis of clinical disease in allograft recipients, when they found CMV inclusion cells in the lung and other tissues of patients who died of pneumonia after transplantation. This relationship has been frequently confirmed and in some surveys, including our previous study, infection rates of 70–90% have been established.[2,8,30] The common finding of CMV in asymptomatic patients after transplantation has suggested that CMV may be an incidental finding in such patients. On the other hand, CMV infections have been implicated in the triggering of rejection episodes,[7,30,48] in the pathogenesis of mild febrile illnesses,[9,11] hepatitis,[3,11,12] pneumonia[16,42,47] and even in the pathogenesis of death. This study represents part of a continuing[29–31] effort to critically analyze the role of these latent viral infections in transplant patients, and to correlate the viral infections with the clinical picture.

Materials and Methods

The procedures for the selection of donors and recipients, techniques of transplantation, standard immunosuppressive regimens, and diagnosis and standard treatment for rejection episodes have previously been described.[46] Briefly, the immunosuppressive regimen in-

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cluded methylprednisolone (20 mg/k) on the day of, and the two days after transplantation. Antilymphocyte globulin (ALG) (20–30 mg/kg) for 14 days after surgery, and decreasing amounts of azathioprine and prednisone to maintenance doses (Figs. 2, 4). The study group consisted of 132 patients who had received renal allografts at the University of Minnesota Hospitals. 113 of these patients were studied after transplantation and 19 patients were chosen at random before the transplant for serial study through the pretransplant dialysis and posttransplant course.

Viral studies were carried out either at the clinical virology laboratory of the University of Minnesota or in the virus laboratory of the Minnesota Department of Health. Fresh urine, sputum, blood, and stool samples were collected for viral isolation weekly for two to six weeks after the patient was placed on the study, and then once every two to four weeks thereafter. Serum was collected for antibody determinations at the same intervals. The methods of specimen collection, processing, and inoculation were as previously described.[5,3] Viral isolates were identified by neutralization according to the usual methods[28] with antisera provided by the National Center for Disease Control, Atlanta, Georgia. CMV isolates were identified by: 1) characteristic cytopathic effect; 2) growth only in human embryonic diploid fibroblast cell cultures; 3) complement fixation (CF) using the patient's isolate as antigen and human convalescent CMV antisera known to be negative for CF antibodies to *Herpesvirus hominis* and varicella-zoster viruses, also supplied by the National Center for Disease Control; and 4) indirect immunofluorescence using convalescent human CMV antisera.

Complement fixing CMV antibody titers were performed in a microtiter system according to standard methods[28] using the AD-169 strain of CMV obtained from Microbiological Associates, Bethesda, Maryland as antigen. The antigen for the varicella-zoster complement fixation test was also obtained from Microbiological Associates, and the *Herpesvirus hominis* type 1 CF antigen was obtained from Flow Laboratories, Rockville, Maryland.

A significant febrile episode was defined as a temperature of 101 F orally for two or more days within a seven-day period. Leukopenia was defined as a total peripheral white cell count less than 5,000 cells/mm^3 for a period of at least two days. Clinical laboratory evidence of rejection was defined as an increase in the serum creatinine level of at least 0.5 mg/100 ml. The patient was considered to have a viral infection if a virus was isolated from any cultured material or if the patient demonstrated a fourfold or greater rise in any of the viral antibody titers measured.

Serial immunologic studies were performed on 61 of the 132 patients. Serum and heparinized blood were collected at weekly intervals during the two to four weeks after the patients were started on the study and then once every four to eight weeks thereafter. Cell-mediated immunity was assayed by *in vitro* lymphocytic responses to phytohemagglutinin (PHA) using the micro-PHA test described by Park and Good[35] and a commonly used macro-PHA test.[15] The micro-PHA test utilizes heparinized whole blood and gives a quantitative estimate of the patient's thymus dependent cell (T-cell) function in peripheral blood. Since the test is conducted in the patient's own serum, lymphocytic responses, as well as serum factors which may affect their responses, contribute to the final result. The macro-PHA test was carried out with slight modifications of a previously described method.[15,31]

Results

Herpesvirus Isolation and Seroconversion

Although the virologic methods used in this study are capable of isolating many viruses, only members of the herpesvirus group, namely, cytomegalovirus (CMV), herpes zoster virus (HZV), and herpes simplex virus (HSV) were consistently isolated. A poliovirus was isolated from each of two patients but these isolations could not be repeated one week later and clinical manifestations were not associated with the isolation. Parainfluenza and adenovirus I were also isolated on single occasions and were not associated with clinical syndromes. Several patients had hepatitis associated antigen in their serum, but as others[40,50] have observed this is not usually associated with clinical symptoms or alterations in liver function in transplant patients.

Table 1 details the herpesvirus infections detected in the study group. Of the 132 patients studied, 110 (83.5%) had laboratory evidence of at least one infection with a herpesvirus whereas the remaining 22 (16.7%) had no evidence of a virus infection. Since 113 of 132

TABLE 1. *Cytomegalovirus and Other Herpesvirus Infections in 132 Renal Transplant Recipients*

No Infections (22)		Herpesvirus Infections (110)	
Early transplant failures	6	Cytomegaloviruses*	
No infections	16	Time of infection obscure	43
		Onset of infection detected	46
		Other complications	10
			99
		Other herpesviruses	11
Totals	22		110

* Twenty-three of these patients had cytomegalovirus infections plus other herpesvirus infections, 18 had cytomegalovirus plus herpes hominis, 3 had cytomegalovirus plus varicella zoster, and 2 had cytomegalovirus, herpes simplex virus and herpes zoster infections.

patients were admitted to the study because of clinical symptoms of various types, a truer incidence of virus infections was determined using the group of 19 patients selected at random before the transplant and studied at intervals before and after transplantation. Sixteen (84.5%) of these 19 had at least one infection with a herpesvirus; 14/19 (74%) had a CMV infection, 4/19 (21%) had a HSV infection, and 1/19 (5.3%) a HZV infection. The incidence of herpesvirus infections in the small group of patients chosen at random is surprisingly similar to the larger group of selected patients (Table 1).

Twenty-three of the 132 study patients had infections with two or more herpesviruses; 18 patients had CMV and HSV infections, three had CMV and HSV infections and two had CMV, HSV, and HZV infections (Table 1).

Cytomegalovirus Isolation or Seroconversion

The remainder of the results will focus only on those patients with cytomegalovirus. Diagnosis of CMV infections was based on the isolation of virus in 72/99 cases (10/14 in the random cases). The diagnosis was based on serological evidence alone in 26 of the 99 cases (4/14 in the random cases). Sixty-six of the 72 cases in whom virus was isolated showed seroconversion to CMV by a fourfold increase in complement fixation titer. CMV was isolated from the urine alone in 23 patients, from the sputum (or from bronchoscopic washings) alone in 13 patients, from the urine and sputum in 33 patients, and from biopsy or autopsy tissue alone in 3/72 patients in whom virus was isolated. CMV was, therefore detected in the urine of 56 of the 72 patients in whom virus was isolated. Of the 56 patients who showed viruria, 44 (78.5%) continued to excrete virus in their urine for at least five months after seroconversion and at least one patient for 12 months. Reappearance of viruria was seen one or more years posttransplant in several patients with high (>1/256) serum titers of complement fixing antibody.

Clinical Manifestations of Cytomegalovirus Infections

Uninfected Patients. Only 22 of the 132 study patients showed no laboratory evidence of viral infections. Six of these 22 patients either had technical complications or were not studied long enough to be included in this analysis. Of the 16 remaining patients, three were among the 19 selected at random who were studied serially before and after they received their transplant. Eight of the 16 patients have remained free of detectable virus infections for six consecutive months after receiving the transplant and two have remained virus free for 20 consecutive months. Only 7/16 virus-free patients had a rejection episode and only 1/16 had the syndrome of fever, leukopenia, and clinical rejection.

CMV Infected Patients. Ninety-nine patients had laboratory evidence of CMV infections. The clinical-virological correlations were obscured in ten patients who had obvious bacterial or technical complications; these ten patients have, therefore, been excluded from the following discussion of clinical correlation. In addition, the time of onset of viral infections could not be determined in 43 of 99 patients with CMV infections who were found to have complement fixing (CF) antibody titers ≥16 when first studied (28/43 patients whose CF antibody titers were high when first studied were also excreting CMV). Although fourfold or greater increases in CF antibody titers were detected in these 43 patients the exact time of onset of seroconversion could not be determined since the titers were already rising when first studied. Clinical correlations in these patients will be discussed below.

Forty-six of the 99 patients in whom CMV infections developed were studied early enough and thoroughly enough to accurately determine the time of onset of their infections. Onset of virus infections was defined as a positive culture after several (at least three) attempts had been negative, or a fourfold or greater increase in CF antibody titer when the initial titer was ≤8. Negative cultures were not detected prior to the positive cultures found in 10 patients. In each of these patients, seroconversion alone was used to determine the time of onset of virus infections. In six patients, serum antibodies to CMV never developed and onset of infection in these patients was determined by the first positive culture after several attempts had been negative. In 45 of these 46 well-studied patients, clinical findings could be correlated with the onset of virus infections, whereas in only one case the initial isolation of virus or seroconversion was not associated with any clinical illness. Eleven of these 46 patients were among the 19 patients selected at random.

Thirty-three of these 46 patients (14 of the 15 randomly selected patients) with laboratory evidence of CMV infections had fever (defined as an oral temperature greater than 101 F for 2 days in any 7-day period) whereas only four patients without a virus infection had such febrile episodes after receiving a transplant. The average time after fever for seroconversion was 29.7 days. The average time after fever and before the first positive CMV culture was 18 days. Each patient was his own control since 27 of the 33 patients were afebrile during the period after transplantation and before the febrile episode later associated with the virus infection.

Only two patients had positive viral cultures three and 21 days before the febrile episode. Positive cultures were collected three to 11 days after the onset of fever in only 8/31 patients from whom virus was isolated. Although CMV could sometimes be isolated at the time of onset of fever or shortly thereafter, the average time of viral isolation was only four days before seroconversion. Since a rise in CF antibody cannot normally be detected until 14 to 28 days after clinical infections,[10,23] seroconversion appears to be a better indicator of the onset of virus infection than isolation of the virus.

CMV infection was also shown to be associated with episodes of leukopenia (defined as a total peripheral leukocyte count less than 5000/mm^3 for two or more consecutive days). Thirty of the 46 patients (8/15 randomly selected patients) with laboratory evidence of CMV infections developed leukopenia; whereas only one of the patients without virus infections was leukopenic after transplantation. Thus, of 31 cases with leukopenia, 30 had laboratory evidence of CMV infection. Onset of leukopenia preceded seroconversion by an average of 30.0 days. In seven patients a rise in antibody titer preceded leukopenia by 4, 6, 7, 28, 57, 61, and 118 days. The average time from onset of leukopenia to positive culture was 12.1 days. Leukopenia followed the first positive culture in five cases by 2 and 12 days and in one case by 132 days. Many of these patients had several leukopenic episodes after the onset of the virus infection and while they continued to have high antibody titers and to excrete virus. However, no other episodes of leukopenia were detected in these patients between the date of transplantation and the onset of CMV associated leukopenia.

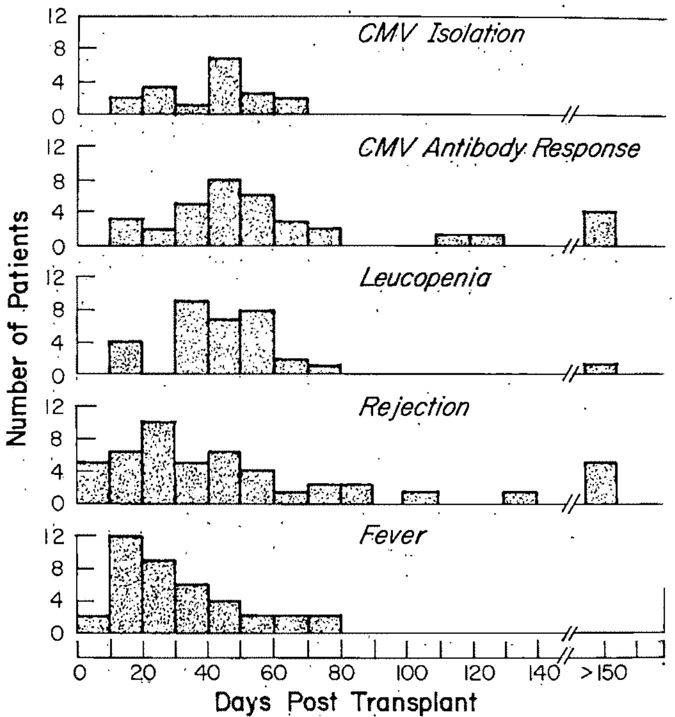

FIG. 1. Composite clinical course of 46 renal transplant patients with known time of onset of cytomegalovirus (CMV). Fever, renal malfunction and leukopenia are followed by the development of antibodies to CMV. Viral isolation is not always possible until seroconversion occurs.

An association between CMV infections and episodes of elevated serum creatinine was also evident. Thirty-seven of the 46 patients (7/15 randomly selected patients) with laboratory evidence of CMV infections had an episode of clinical "rejection" whereas only 7/16 control patients without virus infections showed signs of rejection. Thus, of 44 patients with rejections, 37 had CMV infections. Only one episode of allograft rejection occurred during the period of time after transplantation and prior to the virus associated rejection episode. The average time after rejection for seroconversion was 20.0 days. One patient had his first rejection episode 107 days after the onset of the virus infection and long after his antibody titer had become elevated. CMV was isolated from 32 of the 37 patients, an average of 26.6 days, after rejection. Of the 32 patients virus was isolated *after* the onset of rejection in 19. In six patients the virus was isolated during the first 3 days of the rejection episode and in 7 others the virus was isolated 162, 121, 24, 18, 12, 3, and 2 days before the onset of rejection. Thus, in only 13 patients could it be said that the *virus appeared* prior to or simultaneously with a rejection episode.

Of the 46 patients with known time of onset of CMV infections, 5 developed fevers without clinical rejections, 8 had clinical rejections without febrile episodes, 29 developed both fevers and clinical rejection, and only 4 had neither clinical illness associated with their virus infections. Whether the rejection episode occurred in conjunction with a febrile episode or not, the fever was always closely correlated with laboratory evidence of virus infection. Of the 29 patients who developed both fevers and rejection in association with CMV infection, 22 (76%) developed their initial fevers before or on the same day as the rejection episodes.

The typical syndrome can be seen by examining the frequency distribution of times after transplantation that fever, leukopenia, elevated serum creatinine, and laboratory evidence of CMV infection appeared (Fig. 1). Laboratory diagnosis of CMV infections were made in highest incidence between 30 and 70 days after transplantation, and shortly after the peak incidence of fevers, leukopenia and renal functional deterioration.

The clinical course of a typical patient with this syndrome is shown in Fig. 2. Spiking fevers were followed by renal functional deterioration and leukopenia. CMV infection was demonstrated by a rise in CF antibody titer within 2 weeks and virus was isolated from urine.

Biopsy of the donor kidney at the time of elevated serum creatinine revealed histological changes consistent with classical rejection (Fig. 3). Treatment with increased doses of steroids and local irradiation was undertaken and fever, leukopenia and elevated serum creatinine levels returned to normal. Biopsies of the renal grafts of seven other patients with concurrent infection and elevated serum creatinine were all consistent with rejection, and immunofluorescent studies revealed no evidence of virus-complex nephritis.[27] Culture of 7 of the 8 biopsies revealed no evidence of viral infestation of the kidney itself.

Of the 37 patients whose onset of CMV infection could be determined to be associated with rejection episodes, 35 were given anti-rejection therapy consisting of graft irradiation and steroids.[7] Two kidneys regained normal function without treatment and four kidneys were lost despite treatment. These latter four kidneys demonstrated changes perfectly compatible with rejection.

Two patients were not treated for the elevated serum creatinine. When serum antiviral antibody reached a high titer, serum creatinine and temperature spontaneously returned to normal levels and remained there.[30] No renal biopsy was performed in these patients.

Forty-three additional patients had laboratory evidence of viral infections but the precise time of onset of the infection could not be determined since seroconversion had already occurred. Of these 43 patients, 18 (42%) had fever, 14 (33%) had leukopenia and 25 (58%) had rejection episodes associated with the diagnosis. It is impossible to determine whether the lower incidences of these clinical findings are related to the effect of pre-immunization against CMV or later diagnosis but it is clear that CMV infections were frequently associated with fever, leukopenia and clinical rejection episodes. Three of these 25 patients with rejection episodes have lost their kidneys by rejection.

Cytomegalovirus (CMV) infections occurred in the absence of other obvious complications in 89 patients. Six of these 89 patients died within one month of the diagnosis and none of the other 83 patients died within three months of the infection. Thus, 83 of the 89 patients recovered. The fever appeared self-limited in these 83 patients and usually abated after several days—to several weeks associated with the development of high complement fixing (CF) antibodies against the CMV virus. The leukopenia was usually short-lived and the white blood count reversed to normal after cessation of azathioprine (Fig. 2). Patients who died had persistent fevers (Fig. 4) and prolonged or repeated episodes of leukopenia despite cessation of azathioprine.

A total of 7 kidneys were lost by rejection within three months of the initial rejection episode associated with CMV diagnosis. All these 7 patients survived and were returned to dialysis. All 7 patients developed high antibody titers to CMV.

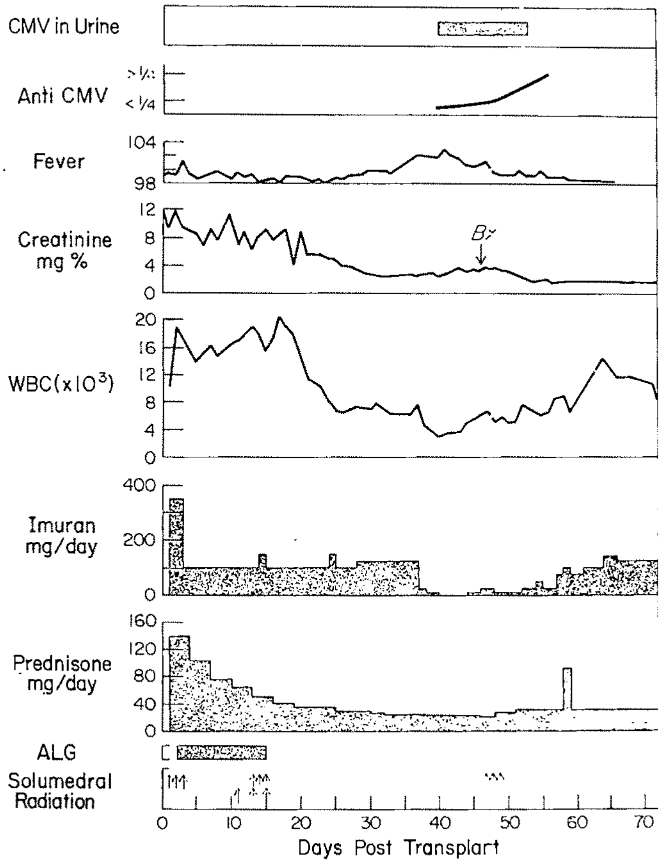

FIG. 2. Clinical course of a patient with typical CMV associated rejection reaction. Daily spiking fevers in the 5th posttransplant week were followed by leukopenia and elevated serum creatinine levels. Renal biopsy (Bx) demonstrated a typical acute rejection reaction (Fig. 3). Leukopenia abated when azathioprine was stopped, and the repection was reversed by increased steroids. The fever resolved as antibody to CMV developed. CMV was isolated from the urine.

Of the 43 patients who had laboratory evidence of CMV infections when first studied and who had seroconverted, none died within three months after the CMV diagnosis was made. In contrast, of the 46 patients whose onset of infection was detected before antibody titers to CMV were detectable, 6 died—all within one month of the diagnosis of the infection by viral isolation. Only one of these 6 dead patients demonstrated a fourfold increase in antibody titers to CMV. The single seroconverter had a titer of 64 on the day prior to death. Histological examination of the kidneys of these six patients, revealed no evidence of rejection despite the fact that renal functional deterioration had occurred in the month prior to death and all patients had required hemodialysis.

Thus, two clinical syndromes seem to be associated with CMV; fever, leukopenia, renal functional deteriora-

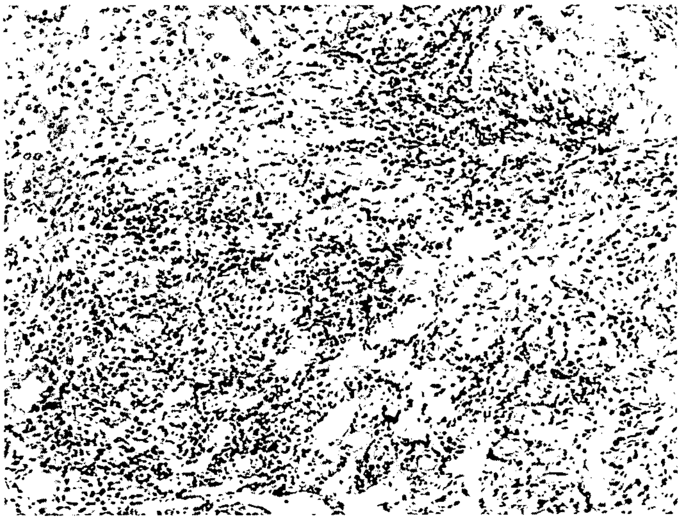

FIG. 3. Renal biopsy specimen from patient whose course is shown in Fig. 2. The biopsy was taken when the serum creatinine was elevated. CMV could not be isolated from the biopsy specimen although CMV could be cultured from the urine. Immunofluorescent studies revealed no evidence of immune complex disease. The picture is compatible with the diagnosis of renal allograft rejection.

tion occur in each. Biopsies suggest that the renal functional deterioration in the patients who survive is associated with histologic evidence of rejection. The patients who survive develop high antibody titers against CMV. The patients who go on to die, have normal kidneys despite clinical evidence of renal malfunction and do not develop antibodies to CMV.

The course of a typical lethal CMV infection is shown in Fig. 4. This lethal viral infection characteristically begins with spiking fever associated with mild generalized malaise; during this prodromal period bacterial and fungal cultures of blood, urine and cerebral spinal fluid are negative and no cause for the febrile episode can be identified. Prostration and orthostatic hypotention usually force the patient to be on permanent bedrest during the next 6 to 7 days. Lymphopenia, thrombocytopenia and mild deterioration of renal function are present. Mild arterial hypoxemia (pO_2 75 mmHg), not usually associated with radiological evidence of lung pathology, is also usually present from the onset of the febrile illness.

In the second week of the syndrome, new symptoms such as anorexia, nausea, vomiting, constipation, and abdominal pains appear. During this period, severe muscle wasting, peripheral edema, and lethargy are characteristic. A more severe arterial hypoxemia (pO_2 40–60mmHg at room air) is present. At this time, microscopic analysis of bronchial washing obtained at bronchoscopy may demonstrate the virus; still there is no other clinical evidence of lung pathology. The thrombocytopenia and lymphopenia persist, and, in 50% of the cases, leukopenia less than 5000 is present. Concurrently, laboratory evidence of moderate liver dysfunction and further deterioration of renal function appears. Except for the possible isolation of the CMV in biopsy specimen (kidney, bone marrow) bacterial and fungal cultures continue to be negative despite persistent high spiking fevers. The fevers are difficult to control by external cooling or anti-pyretics.

In the third week, there is a further deterioration of the patient's general condition. Muscle wasting is now more evident, peripheral edema is more marked, and icterus may be clearly evident. The severe hypoxemia, now requiring continuous O_2 therapy, is now associated with X-ray evidence of interstitial pneumonitis in about half of the cases. Liver and renal function further deteriorate (bilirubin >3mg%, SGOT, SGPT elevation in 75% of the cases and hemodialysis required in 75% of the cases). Hyperamylasemia associated with abdominal distention, decreased bowel sounds, diffuse rebound and tenderness is usually present in 50% of the

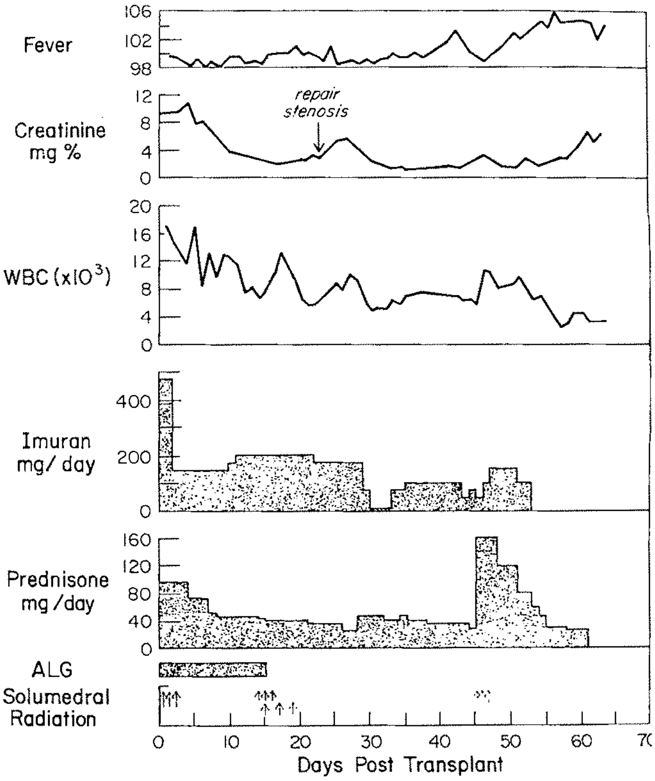

FIG. 4. Clinical course of a patient with CMV infection leading to death. Hypertension and renal malfunction was treated in the third posttransplant week with steroids and graft irradiation. Subsequently renal artery stenosis was repaired. Spiking fevers in the 6th posttransplant week was followed by renal malfunction and ultimately leukopenia. The fevers persisted until death. Bacterial and fungal cultures were repeatedly negative until the week prior to death. No antibodies to CMV were found. At autopsy there was no evidence of allograft rejection in the transplanted kidney.

patients. In these cases, diagnostic peritoneal lavage is sterile.

Characteristically, it is during this period that the majority of the patients (75%) presents evidence of CMV infection in cultures of sputum, urine, bone marrow and kidney biopsy; bacterial cultures negative until the third week now become positive for members of the intestinal flora.

In the terminal phase, lasting usually 5–8 days, there is further progression of the symptomatology. The patient is now semicomatose, with rapid progression to deep coma. High fever, arterial hypotention, labored respiration, tachycardia disproportionate to the degree of fever, and emaciation are present.

Periods of apnea develop early during this period requiring constant assisted mechanical ventillation, Icterus, petecchiae, ecchimosis, GI bleeding are a reflection of the further deterioration of the hepatic function. Hypofibrinogenemia, prolongation of PT, PTT, severe thrombocytopenia, uremia, all contribute to the hemorrhagic manifestation. The severe leukopenia (less than 2000mm^3) still associated with lymphopenia contribute to the terminal bacterial and fungal invasion. Irreversible pulmonary edema represents the terminal event.

At autopsy severe malnutrition, edema, petichiae and loss of subcutaneous fat are always present. Pneumonitis and pulmonary edema are universally present along with CMV inclusion bodies in the lungs. CMV can be cultured from multiple tissues, as can aspergillus fumigatis and a variety of gram negative organisms. Bile stasis, congestion, plasma infiltration and fatty metamorphosis as well as CMV inclusion bodies are found in the liver. The GI tract shows evidence of diffuse ulcerations. The kidneys show no evidence of acute rejection though CMV inclusion bodies can be found and CMV cultured.

Immunologic responses of patients who recovered from the virus infections differ markedly from those patients who died. The micro-PHA stimulation responses of 61 patients stabilized on maintenance doses of azathioprine and prednisone had mean responses of 1436 ± SD 1708 CPM. This mean response is greater than two standard errors below the mean of the normal ($p < .0001$). The patients who had recovered from viral infections had a mean response of 1556 CPM which is not significantly different from the entire patient group or a group of eight patients who never developed virus infections, (1547 CPM). In addition, significant changes in the micro-PHA responses, attributable to the CMV infections, were not detected during the course of those infections.

In contrast, the mean micro-PHA response of four carefully studied patients who died of CMV infections was less than 400 CPM throughout their course. They showed no increase in PHA responses when immunosuppression was reduced or even stopped. In addition, their kidneys showed no evidence of renal allograft rejection at postmortem examination despite long periods off the immunosuppression prior to death. Low micro-PHA responses, however, could not always be correlated with increased susceptibility to severe infection or failure to reject renal allografts. Thus, it was not unusual for patients whose clinical courses were free of serious clinical infection to have periods of weeks with equally low responses. In this latter group, however, micro-PHA responses eventually rose to levels equalling or exceeding mean responses for patients on maintenance doses of immunosuppressive therapy. Also, rejection episodes occurred in these patients despite moderately low micro-PHA responses.

The macro-PHA test tests the function of washed lymphocytes in the absence of blood. The average response of the immunosuppressed renal transplant patients on maintenance therapy was 50,283 CPM, while the average response during the first two weeks after transplantation was 46,895 CPM (normal 48,456). These responses can therefore be considered normal. One of the four patients who died and who demonstrated a micro-PHA response of only 95 CPM four days before death, had a macro-PHA response of 45,478 CPM on that same day.

Complement fixing (CF) antibody responses to CMV of the surviving patients were usually ten to 100 times higher than those found in non-immunosuppressed patients. Others have reported[48] that normal patients infected with CMV respond with titers of 1:16 to 1:64. We have observed rises in antibody titer of this same magnitude in non-immunosuppressed patients infected with CMV. Of the immunosuppressed patients who produced CF antibody to CMV, 95% had antibody titers of 1:64 or greater. The patients who died did not respond with CF antibody to their CMV infection throughout their long clinical course.

Discussion

Cytomegalovirus (CMV) infections have been frequently observed in patients receiving organ transplants since the Denver group first described this phenomenon in 1964.[17] Hill *et al.* discussed 15 patients with evidence of CMV infection at autopsy out of a total of 32 patients who had died after receiving transplants.[7] Evidence of infection was found in the lungs as well as other organs. These observations have been repeatedly confirmed.[2,3,8,11,12,16,30,41,42,50] CMV in transplant patients can be most easily recovered from the urine but frequently also from the sputum or from bronchoscopy specimens. In our experience, viremia, even utilizing cultures of buffy coat, has been difficult to detect. The fact that antibodies to CMV appear 3–4 weeks after a febrile illness but only a few days after viral isolation strongly suggest that viremia occurs but is not being detected by our current techniques. In any case, we can confirm the fact that CMV infections occur in 70–90% of renal transplant patients.

Laboratory evidence of CMV infections is so common in asymptomatic transplant recipients, that it has been regarded as an incidental finding. However, our continuing epidemiological studies in this patient population demonstrate that the first appearance of CMV is almost always accompanied by a clinical illness.[29,30] The most characteristic and frequent picture of CMV infection seems to be the appearance several weeks posttransplant of fever, leukopenia, and signs of renal functional deterioration. The fever is the first sign, most often followed sequentially by leukopenia and renal malfunction. Biopsies of kidneys reveal typical features of rejection and the absence of immune complex disease and/or gross infection of the kidney itself. In fact, kidney biopsies failed to produce evidence of virus infection in almost all circumstances, even though the urine was the most common source of isolated virus. The rejection reaction responds to antirejection treatment, leukopenia responds to decreases in azathioprine dosage and the fever abates as antibodies to CMV develop. Recovery is the general rule though irreversible kidney rejection may appear.

Six of our patients died within one month after the laboratory diagnosis of CMV infection. The clinical characteristics of these patients do not differ during the early phase from patients who recover—fever, leukopenia and renal functional deterioration are also present. Certain differences can be detected, however. The six patients had little histological evidence of rejection within the malfunctioning kidney, antibody to CMV did not usually appear, and the lymphocyte responses to mitogen, though intact, were suppressed in the presence of whole blood.[31] In short, evidence of immunologic reactivity was lacking. This difference in immunologic responsiveness between patients who recover and those who die when infected with CMV is in harmony with findings that CMV itself is a profoundly immunosuppressive virus.[20,21] Howard *et al.* found that CMV-infected mice could not reject skin grafts or respond to sheep red blood cells (SRBC) until recovery had occurred. The patient already immunosuppressed with antilymphoblast globulin, azathioprine, prednisone, radiation, and methylprednisolone appears to be even more profoundly depressed by CMV infections. Such patients appear susceptible to superinfection with gram negative bacteria and other opportunistic organisms which sequentially infect and ultimately kill the patient. At autopsy a "mixed" infection is frequently found[45] but evidence of organisms other than CMV is usually lacking until the preterminal phase of illness when blood and sputum cultures finally became positive for bacteria.

There are a number of problems unresolved by these studies. The first is the source of CMV: A number of epidemiologic studies have suggested that CMV infections are common in early neonatal life and that most patients will have evidence of antibodies to virus by adult life.[26] The virus, however, appears to remain within the body in latent form, and can be reactivated despite the presence of high complement fixing or neutralizing antibody titers.[51] Alternatively, CMV infections in transplant patients may be acquired from the environment, transfusions,[39] or even the donor organ itself.

It is, however, generally difficult to culture CMV from bank blood.[34] The virus, when present in blood, is most easily found in the leukocytes and transplant patients are given only leukocyte poor or frozen blood. Similarly, cultures of donor kidneys have not revealed virus. In short, reactivation of latent endogenous virus is the most likely route of infection.

Studies are currently under way to strain-type CMV isolates from our renal allograft patients and to determine differential neutralizing and complement-fixing titers to the various strains isolated. This should enable us to determine whether sequential CMV infections are acquired from exogenous sources, or result from reactivation of endogenous, latent virus.

We have previously discussed the complex interrelationships between reactivation of latent viral infections, immunosuppression, and allograft rejection.[30] On one hand, it is possible that a rejection episode might activate a latent virus infection.[30] Activation of a latent herpesvirus infection has been demonstrated in rabbits[14] in conjunction with anaphylactic shock, or a second exposure to the antigen. Graft versus host reactions have also been shown to activate latent viruses.[4,18,19] Other studies have shown that lymphocytes, transformed by mitogens or antigens, can be more easily infected than can normal lymphocytes, and such cells appear to support viral multiplication much better than do nontransformed cells.[24] It seems likely that lymphocyte transformation is an integral part of the rejection process; thus, recently transformed lymphocytes would be available for virus infection. Therefore, clinical or subclinical, rejection occurring soon after transplantation might activate a latent CMV infection.

The second possibility is that virus may act as a nonspecific stimulus or adjuvant upsetting the very delicate immunologic balance between donor organ and host. The postulate presupposes that there is a state of subclinical rejection present in most allografted kidneys and that a state of relative immunologic adaptation of host to graft becomes established with time. Random biopsy specimens of well tolerated allografts usually show some evidence of rejection, however minimal.[13,38,43] In addition, humoral and cell-mediated immunity to functioning allografts have been repeatedly demonstrated.[13,33,36,37,44] Similarly, there is much evidence to support the idea that bacterial agents (i.e. endotoxin, BCG, infections) can nonspecifically stimulate immunologic processes.[52] Endotoxin, for example, can facilitate the rejection process itself.[1] Perhaps viruses, too, or virus antibody interactions can do likewise. This possibility receives further support from patients with postperfusion mononucleosis caused by CMV. In these patients delayed hypersensitivity to ampicillin and other immunologic abnormalities developed concurrent with their virus infection.[22,25] Furthermore, if we can compare this clinical syndrome to postperfusion mononucleosis, "exposure" to infectious doses of virus precedes clinical rejection by about 2 to 4 weeks. Although one cannot say that infection triggers rejection just because it precedes it, these data lend added weight to this possibility. Further weight in support of this hypothesis derives from the fact that lethal CMV infections are not associated with histological evidence of rejection despite renal malfunction. In these patients, it is unlikely that rejection reactivates the virus, but that the virus is reactivated by immunosuppressive drugs.

In sum, two paradoxical responses to the virus are possible. The relatively immunocompetent transplant recipient behaves as though the virus were an immunologic adjuvant triggering an allograft rejection. The immuno*in*competent patient may be further immunosuppressed by the virus and develop sequential opportunistic infections and die. These paradoxical responses to CMV virus have been reproduced by Howard *et al.* in the murine CMV model (Howard, unpublished observations). A primary CMV infection in a mouse is immunosuppressive, and the mouse cannot reject skin allografts or make antibody to SRBCs. Mice who are immune to CMV, have accelerated responses to primary allografts and better antibody responses to SRBC if primary antigenic challenge is accompanied by a second CMV inoculation. If these results are applicable to the clinical situation, we might expect that CMV infections were primary infections in those patients who died, and were secondary or reactivation of latent virus in the patients who survived.

The profoundly immunosuppressed state of patients with potentially lethal infections, and the absence of histological rejection reactions should permit the rational administration or withholding of antirejection therapy in these cases. Within a few days after development of fever and renal malfunction, PHA responses in autochthonous plasma and renal biopsy can be performed. If renal allograft rejection is shown in the biopsy and PHA responses are normal, one might assume that the self-limited viral syndrome is present. On the other hand, if a typical viral infection is accompanied by renal malfunction but a normal kidney biopsy and PHA responses are depressed, immunosuppression might be stopped and the patient allowed to recover.

The causes of renal malfunction in the lethally infected patient are not totally clear. These patients appear to be hypotensive, vasodilated and edematous. In this state of chronic viremic shock, renal perfusion may be inadequate to maintain adequate function. Alternatively, the kidney could be infected by the virus itself which shows a propensity for epithelial tissues. Bone *et al.*[6] have recently reported that kidney biopsies in febrile leukopenic CMV infected transplant patients showed tubular cell degeneration and intracytoplasmic viral bodies.[6]

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DISCUSSION

DR. RICHARD E. WILSON (Boston): I'd like to first discuss the question of disease and syndrome incidence.

Dr. Simmons attempted to perform what is called by the epidemiologists a prospective cohort study in 19 control patients which he mentions in the manuscript; here one starts with exposure and looks for disease.

We would like to know what percentage of transplant patients exposed to CMV disease developed it, and what percentage of these identified as having CMV developed the true syndrome that he mentions? Unfortunately, the 19 patients is a small group, but maybe he can tell us what has actually happened to those 19 people that he looked at prior to transplant.

It's difficult to compare those with 110 patients who actually had CMV disease, and then were looked at in retrospect.

The other approach is to do what's called a case control study, which starts with the syndrome, looking for CMV disease; in this you need a control group of transplant patients with the same complaints to determine whether or not they actually have this disease.

I don't think these data can answer these questions exactly, as to whether CMV is the cause of the complaint, rejection or lethality. I think a much larger prospective look at their transplant population will be necessary, and I hope they will do this, because they have developed these investigative tools, which are so necessary.

I'd like to focus on the question of the adjuvant effect of CMV infection on allograft rejection. We and others have noticed for many years that reducing or stopping immunosuppressive therapy to permit survival from severe pulmonary infection of all etiologies has almost always been associated with a rejection episode, while, interestingly, cessation of Imuran for hepatic toxicity or hepatitis rarely results in such a rejection. From the diagrams he shows in the manuscript, the cessation of Imuran, followed by rejection and the onset of CMV titer could all be the result of reduction of Imuran alone, with some unidentified viral agent giving the complaint, not necessarily the CMV virus.

Also in the chart of the lethal patient that he showed, it does not necessarily follow that this was due to CMV death; rather, a marked increase in immunosuppression, with wasting and lethality related to that, and the CMV virus being a concomitant.

What I'm really asking is: Is there a difference in the way the patients were treated, especially the ones who got the rejection episodes? Were their immunosuppressive agents reduced significantly, and, conversity were all of the patients who died those who had immunosuppression greatly increased, as part of the management of their disease?

DR. THOMAS C. MOORE (Torrance, California): We, too, have been concerned with the problem of the high incidence of cyto megalovirus—CMV—infection in renal transplant patients. Dr. Milan Fiala, of the Infectious Disease Service of the Harbor General Hospital, has been conducting a collaborative study relating to this problem for some time now with our renal transplant unit at UCLA Harbor, and the unit of Drs. Berne and Payne at USC County.

(Slide) In a retrospective six-month-long study of 35 recipients, viremia was found in 43%, viruria in 66%, and complement fixing antibody rise in 26%, with an overall evidence of active CMV infection of 76% of recipients.

The incidence of viremia was significantly higher, 52%, in patients studied within one year of transplantation in comparison with those studied two years after transplantation, where it was only 16%. All 15 patients with arthralgia had active CMV infection. The incidence of other viral infections was comparatively low in this retrospective study.

Since February of 1973 a prospective study, currently involving 26 recipients, has been carried out, starting with the period of pretransplant hemodialysis, and continuing at monthly intervals for four to thirteen months after transplantation.

After transplantation, 38% of these patients had CMV viremia, 50% had viruria, and 77% had a rise in complement fixing antibody, for an overall incidence of active infection of 88%. One additional patient had autopsy evidence of CMV infection in the transplant, but no identification of virus or of seroconversion. Perhaps this patient corresponds to the fatal syndrome referred to by Dr. Simmons.

Reactivation of other viral infections, such as *Herpes simplex, varicella zoster*, adenovirus, measles, Epstein-Barr virus and hepatitis B virus were comparatively low, in comparison to CMV, in this prospective study, but were higher than was encountered in the retrospective study I have just cited.

Of the 26 recipients 20 of the 26 recipients in the prospective study, or 77%, had fever and arthralgia and a combination of other symptoms; chest infiltrate, SGOT rise, with elevated bilirubin levels 2 to 6 mg/%, and transplant rejection episodes.

Eighty-five per cent of the 20 recipients with fever and arthralgia, 100% of the four with chest infiltrates, 100% of the four with elevated SGOT and bilirubin levels, and 95% of the 19 with a rejection episode had active CMV infection. Only one of the four with elevated SGOT and bilirubin levels was positive for hepatitis B antigen.

Eighteen of the 19 recipients with rejection episodes had evidence of active CMV infection. Nine of the 19 with positive viremia studies were studied prior to rejection episodes. Two of these were positive at four and ten days prior to the rejection episodes, and seven were positive only after rejection episodes, these at eight, 11, 13, 28 and 47 days after the onset of rejection.

The fatal syndrome of the six cases cited by Dr. Simmons was encountered in only one of the recipients in our study as I mentioned earlier.

We did have three patients in our study with CMV viremia who had many atypical lymphocytes, with virtual disappearance, to less than five %, of both T- and B-cells. These three recipients did not experience a fatal outcome.

In order to investigate more thoroughly the source of CMV infection in renal transplant recipients, we recently have begun to augment the studies cited above by a study of cadaver donor blood and tissues and a study of Belzer machine plasma perfusates both before and at the end of machine perfusion preservation.

DR. G. MELVILLE WILLIAMS (Baltimore): We have had 16 patients with a diagnosis of cytomegalovirus disease in whom the cytomegalovirus was the chief pathogen involved. In this group of 16 patients, out of the 200 that have been transplanted in the past four years, we have had three deaths. The only death from infection occurring at Johns Hopkins Hospital in the last two years has been in one of these patients. In this group of 16 recipients of cadaveric transplants, only four continue to have functional kidneys. The remainder have had to have immunosuppression stopped and the kidneys have been lost.

What has interested us was the fortuitous finding present in open biopsies in all of these 16 transplants. Drs. Robert Wyllie and Norman Anderson in our laboratory have been fascinated by applying histochemical techniques in the study of transplant rejection. They noted, in the first patient of this series, little red dots which could be viral bodies in the proximal tubules when frozen tissue was stained with methyl green-saphronin. They suggested in this particular patient that we rebiopsy the patient in one month; while this lesion was at first focal, it became apparent that more tubules were involved with time. These little red spots stained positively for DNA, using DNA stains, suggesting that these cytoplasmic inclusions contained DNA and, therefore, added weight to the idea that this was a cytoplasmic phase of a DNA virus.

(Slide) This slide simply shows the degree to which tubular degeneration can be associated with this particular kind of red dot disease. We think that this is probably cytomegalovirus; for in 12 of 12 patients in whom we had sequential sera, there was a very good correlation between this finding and subsequent elevations in antibody two to three weeks later. In eight of the 12 cases, the virus was cultured from the specimen.

We have also worried about the seriousness of this problem. For example, we have screened dialysis patients and have found, not infrequently, patients with rising antibody titers. Should they or should they not be transplanted? One patient in particular was disturbing, for he developed "uremic" pericarditis and tamponade. His pericardium was resected and cytomegalovirus could be cultured from pericardial tissue but not from pericardial fluid.

This is an ubiquitous virus. Therefore, it's very hard to pin down with certainty whether this is indeed the chief pathogenic agent in the viral syndromes reported. However, I think studies such as those performed by the group at Minnesota are contributing to increasing the evidence favoring the concept that this virus in these patients is a major pathogen.

Dr. C. W. Putnam (Denver, Colorado): We can confirm some aspects of Dr. Simmons' very interesting paper.

For example, we have documented that almost every transplant recipient under immunosuppression has evidence, either serologic or by culture, of viral infection, which is often chronic. We would tend to emphasize that this evidence may develop without fever, leukopenia, rejection, or any other significant clinical manifestation. This does not mean, as was Dr. Simmons' main message, that these are harmless infestations.

I hope in the future that at least three questions, which are subtle ones, may be answered: First, does the development of antigen-antibody complexes in these patients occur? And if so, do they contribute to the glomerulonephritis mentioned earlier this afternoon?

Second, what role, if any, does chronic viremia, including viruses other than the Herpes group, play in the increased incidence of malignancy in chronically immunosuppressed patients, particularly the skin cancers mentioned by Professor Ewing of Melbourne?

Finally, I draw your attention to the speculation, published by Corman and others from the Colorado group, that CMV infection of the bile duct epithelium has caused at least some of the biliary obstructions that have plagued efforts at liver transplantation.

Dr. Simmons' paper opens a Pandora's box of possibilities, of which none has been absolutely established, but all of which deserve exploration. The transplant fraternity owes him a debt of gratitude for doing this.

Dr. Richard L. Simmons (Closing discussion): To Dr. Wilson, who wants to know whether these patients are retrospective; of course, it is in part retrospective and partly prospective. At first you study the patients who are ill, then you study the patients who have been transplanted but before they become ill, and finally you start studying those who are not yet transplanted. That's why I focused on the 46 patients who had no evidence of infection in the posttransplant period and who were, in a sense, prospective, but not classically so.

To answer your direct question: What per cent of the patients who were studied prior to transplantation got the virus? Sixteen of 19, 84.5%, of the prospective patients developed the viral infection. Notice that 83.5% of the 132 patients studies over all also had the infection. Thus, the prospective and retrospective studies show remarkably similar results similar to Dr. Moore's 88%, and to 70–90% in the literature. The patients without infections are very important. We almost never see fever or leukopenia in patients without infection despite the fact that there are many other potential causes of fever.

Which comes first, the rejection or the infection? There are a number of pieces of evidence in the literature that rejection can stimulate lymphoproliferations, and that lymphoproliferation can lead to reactivation of a latent endogenous virus. For example, leukemia viruses can be activated by a graft-versus-host disease. Thus, we must assume that rejection can stimulate infection.

But it is also well known that infections can trigger rejection. A beautiful study in our laboratory by Dr. Richard Howard has shown that graft rejection can be accelerated by infusing murine cytomegalovirus into a mouse who is immune to CMV. On the other hand, CMV is a strongly immunosuppressive viral infection if the animal is not previously immune.

Dr. Moore brings up a lot of other problems. We have rarely found other viruses. Unfortunately, we have not looked for Epstein-Barr virus, which has been found very frequently in England. Clinical hepatitis, we think, is very commonly caused by cytomegalovirus, especially in a chronic form long after transplantation even in patients who show high titers of complement fixing antibody against CMV.

Again, the source of the virus is very important. We have cultured bank blood and everybody that has cultured bank blood finds that it's very difficult to culture CMV from bank blood. The virus is in the buffy coat, and can be cultured from fresh blood. The postperfusion syndrome in cardiac patients may be due to CMV in fresh blood transfusion. Culturing of kidney biopsies has failed to reveal the virus, and culturing of the preservation fluid has failed in every case to reveal the virus.

The source of infection may well determine the clinical syndrome seen. It is possible, for example, that the first infection from an exogenous source in a non-immune patient results in profound immunosuppression (as in mice) leading to death. However, if the patient is immune to the cytomegalovirus and reactivates the endogenous virus, the infection may act as a terrific immunologic adjuvant leading to a rejection episode.

Dr. Williams has been smart enough to use a special stain on his kidney biopsies, and probably is demonstrating the cytoplasmic phase of the cytomegalovirus. We're going to try that as well.

Dr. Putnam again raises the question of how frequently we see the virus, and how rarely we see a clinically important syndrome. I think the syndromes are frequently very minor. I do think that if you do the prospective study, it's very likely that you will find fever, at least, very frequently appearing with the virus. He also brings up the possibility that these viruses may be involved in the pathogenesis of cancer. Herpesviruses like CMV are known carcinogens in animals, and are highly suspect as carcinogens in man. Herpesviruses persist in latent form, they cause cancer, and transplant patients have a high incidence of cancer. This relationship obviously needs to be studied further.

BCG Immunotherapy of Malignant Melanoma:

Summary of a Seven-year Experience

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Over the past 7 years, 151 patients with malignant melanoma have been treated with BCG immunotherapy alone or as an adjunct to surgical therapy. Direct injection of metastatic melanoma lesions limited to skin resulted in 90% regression of injected lesions and 17% regression of uninjected lesions in immunocompetent patients. Approximately 25% of these patients remained free of disease for 1 to 6 years. Direct injections of BCG into nodules of patients with subcutaneous or visceral metastases resulted in a lower incidence of local control and no long term survivors. Attempts to improve the results of immunotherapy in these patients by palliative surgical resection of large metastatic lesions to lower tumor burden followed by BCG immunotherapy significantly improved the results although many patients still developed recurrent disease. Early results of a clinical trial combining BCG immunotherapy with regional lymphadenectomy in patients with melanoma metastatic to lymph nodes have been encouraging and promising. Further controlled clinical trials are necessary to elucidate the role of BCG in immunotherapy. However, since BCG is but one of a number of potential immunologic adjuvants, even more effective immunotherapy will be possible as further knowledge of the interactions of cellular and humoral immunity is acquired.

During the past seven years, evidence has accumulated from numerous sources indicating the importance of the immune system in malignant melanoma. Morton and Malmgren's initial description of tumor associated antigens in human malignant melanomas using immunofluorescent techniques were soon confirmed and extended by a number of independent investigators using a variety of immunological techniques.[4,6,7,10,12] The evidence to date implies that malignant melanomas contain tumor specific antigens which elicit the production of circulating humoral antibodies and cytoxic lymphocytes in patients with melanoma.

Furthermore, there appears to be a correlation between the clinical status of the melanoma patient and the incidence of anti-melanoma antibodies in their sera. Patients with a localized melanoma were more likely to have antibody in their sera than those patients with disseminated disease. Also, some patients who were observed frequently throughout their clinical course had the antibody disappear from their sera as the disease progressed.[6,8]

Evidence that manipulation of the immune system can favorably affect the clinical course of patients with malignant melanoma was suggested by our preliminary studies with BCG immunotherapy of malignant melanoma reported in 1970.[8,9] A small series of eight patients with intradermal or subcutaneous metastases were treated by intralesional injections of BCG vaccine, a powerful nonspecific immune stimulant. Approximately 90% of the melanoma nodules directly injected with BCG regressed in patients who were immunologically competent as

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measured by their ability to display delayed cutaneous hypersensitivity to dinitrochlorobenzene (DNCB) or tuberculin. Moreover, the nodules at sites distant from the BCG inoculation also regressed in approximately 20% of patients who were immunologically competent.

These observations of immunotherapy in malignant melanoma by intralesional injections of BCG were soon confirmed by a number of investigators including Nathanson,[11] Pinsky[13] and Siegler.[14] The complete regression rates in all of these series were remarkably constant at 15–25%.

This report summarizes our experience with BCG immunotherapy of malignant melanoma over the past seven years.

Materials and Methods

The patients included in this study were seen by the authors in the Surgery Branch of the National Cancer Institute from 1967 to 1970 or by the Division of Oncology, Department of Surgery, UCLA School of Medicine, from 1971 to 1974. The patients selected for immunotherapy had documented recurrent melanoma, known residual disease, or a high risk of developing recurrence. All patients gave informed consent for experimental immunotherapy.

Each patient was extensively evaluated to stage the disease as thoroughly as possible before immunotherapy was started. This evaluation included a complete history and physical examination, liver function tests, chest x-rays, metastatic bone series, and radioisotopic scans of the bone, brain, and liver. Chest x-rays and liver function tests were obtained at 3 month intervals and repeat liver scans at 6 month intervals or more frequently as the clinical situation dictated.

Immunologic Evaluation

Immunologic evaluations of all patients were carried out by skin testing prior to immunotherapy. Each patient was sensitized using the method of Eilber and Morton by applying 2,000 μg of DNCB dissolved in 0.1 cc of acetone topically to the medial aspect of the arm.[2] A challenge dose of 100 μg of DNCB was applied on the day of sensitization, and doses of 100, 50, and 25 μg were applied to the ipsilateral forearm 14 days post sensitization. After an additional 48 hours, the skin tests were examined and graded. Reactions were quantitated by a hypersensitivity score which was determined by the smallest amount of DNCB that elicited a positive hypersensitivity reaction characterized by erythema with induration extending over one-half of the area of the test site. The patient was considered DNCB positive if the delayed hypersensitivity reaction was present at the 100 μg site.

At the time of DNCB challenge, each patient was also tested for delayed cutaneous hypersensitivity to four common microbial recall antigens. The antigens employed were: mumps, (Lilly 2 units); PPD (Connaught, 5 units intermediate strength); Varidase (Lederle, 10 units); and Monilia antigen (Hollister-Stier, 2 units). All antigens were applied as 0.1 ml intradermal injections in the forearm contralteral to the DNCB test. A response of greater than 5 mm of induration was considered positive.

TABLE 1. *Results of Intratumor Injections of BCG**

Location of metastases	Intracutaneous	Subcutaneous and/or visceral
Number of patients	36	9
Proportion of directly injected metastatic lesions that regressed	684/754–91%	8/26–31%
Patients with regression of uninjected nodules	6/36–17%	0/9– 0%
No evidence of disease	11/36–31%	0/9– 0%

* Followup: 6–74 months.

Immunotherapy

The method for administration of BCG by intratumor injection has been previously described.[2] Briefly, direct injection of intracutaneous and subcutaneous malignant melanoma nodules was performed using 0.1–0.5 cc of Glaxo strain BCG for each lesion.

Systemic immunotherapy was begun for patients with Stage II melanoma from 3–6 weeks following the operative procedure and involved; 1) *BCG* alone (Tice strain, Chicago Research Laboratories) given by the tine technique adjacent to each axilla and groin at weekly intervals for 1 year, biweekly for 6 months, and then monthly thereafter or; 2) BCG plus allogeneic melanoma cells (24 of 67 Stage II patients). In the latter procedure, the BCG was given by the tine technique and 1×10^8 autologous irradiated or allogeneic tissue culture melanoma cells were injected separately at each time interval.

BCG was administered alone or as an adjuvant mixed with tumor cell vaccine to patients with Stage III disease following resection of gross disease at distant metastatic sites. The surgical procedures employed included multiple pulmonary resections (7 patients), small bowel resections (4 patients), splenectomy (1 patient), lymphadenectomy at a site distant from the draining lymph nodes (10 patients), resection of a cerebral metastases in 1 patient, and excision of distant bulky subcutaneous tumor nodules in 16 patients. Surgical procedures in these patients were palliative and designed to lower tumor burden in order to make immunotherapy more effective.

Recurrence and survival rates were analyzed by the actuarial life table method in order to include all patients treated to date.[1] The horizontal axes on these graphs represent the proportion of patients free of recurrence or who survived at each point in time. The number of patients who were free of recurrence or who survived versus the number of patients at risk is given on the graphs at each point.

Results

BCG Immunotherapy by Intratumor Injections

Forty-five patients have been treated with intratumor injections of BCG vaccine for their metastatic disease. The results are summarized in Table 1.

Patients with intradermal metastases who were treated with intratumor injections of BCG were the most likely responders to treatment. Table 1 gives the results in 36 patients treated during the past 7 years. Fourteen patients had in-transit metastases in the same extremity as the primary and 22 patients had distant metastases beyond the primary region. A total of 754 melanoma nodules were injected in these 36 patients and 684, or 91%, of the injected lesions underwent complete regression. In addition, 6 of these 36 patients, or 17%, had regression of uninjected melanoma nodules. A total of 22 uninjected nodules regressed in these 6 patients. Eleven of the 36 patients, or 31%, remained free of disease from 6 to 74 months following BCG immunotherapy.

Three factors appeared to correlate with response to BCG immunotherapy: 1) the location of the metastasis, 2) the amount of tumor present, and 3) the immunocompetence of the patient. Patients with subcutaneous or visceral metastatic lesions had a poor response to BCG immunotherapy. The results in 9 patients are summarized in Table 1. Only 31% of the 26 lesions directly injected with BCG regressed. Complete regression of uninjected lesions has not been observed in patients with subcutaneous or visceral disease and none has remained completely free of disease. However, one patient with liver metastases appeared to have a temporary remission following injection of BCG into subcutaneous metastatic nodules in the neck. This 3 month remission was manifested by weight gain, improved performance status, decrease in the size of liver metastases as measured by liver scan and improvement in liver function tests.

The immunocompetence of the melanoma patient as judged by delayed cutaneous hypersensitivity to DNCB at the time of initial testing or the development of a positive tuberculin reaction and conversion to DNCB positive following immunotherapy correlated well with response to BCG immunotherapy. Most patients who had regression of lesions directly injected with BCG and all of those that had regression of noninjected lesions were immunocompetent on initial testing. Additionally, the few patients who had regression of directly injected lesions who were initially DNCB negative all converted to positive following intralesional BCG.

Sequential biopsies of tumor nodules were obtained in many patients for histopathological studies following immunotherapy. Prior to immunotherapy, biopsy usually showed minimal mononuclear collections adjacent to the melanoma nodule but no infiltration within the tumor cells themselves. Following BCG injection, an intense lymphocytic and mononuclear infiltration usually occurred after 3–4 weeks with destruction of all viable melanoma cells within the melanoma nodule. Serial biopsies of uninjected melanoma nodules following BCG immunotherapy at distant sites frequently showed an increasing mononuclear infiltrate.

BCG Immunotherapy as an Adjunct to Surgical Resection in Patients with Stage III Disseminated Malignant Melanoma.

As a result of the experience summarized above, we concluded that BCG administered by intratumor injection did have activity in patients with advanced disease when the amount of tumor in any one site was small and the disease was limited to the skin. BCG clearly had little activity in patients with bulky disease or those with visceral metastasis. Therefore, we began to investigate the possibility of resecting the large visceral and subcutaneous metastases and administering postoperative

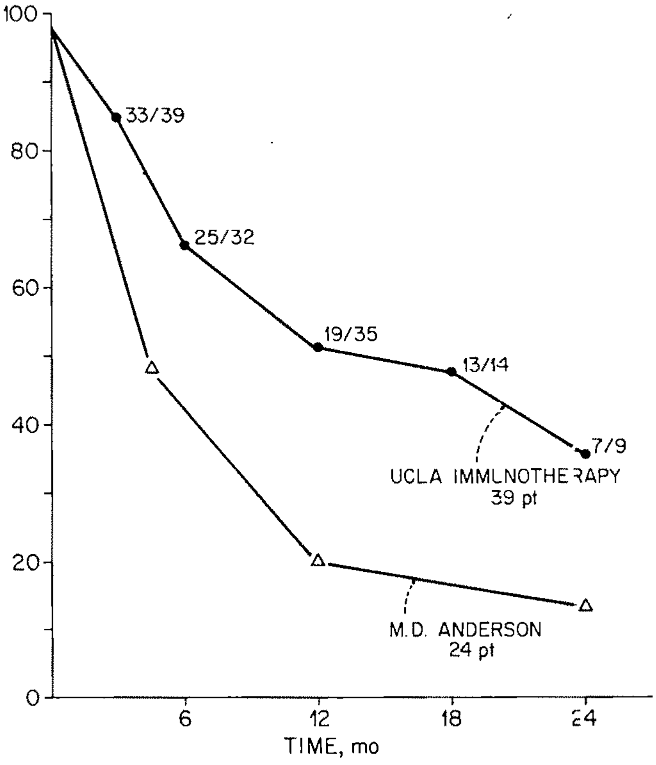

FIG. 1. Recurrence Rate: Stage III Melanoma. Percentage of patients free of recurrent melanoma following surgical resection of all gross disease and postoperative adjuvant immunotherapy. Numbers separated by a slash (/) indicate number of patients who remained free of disease/number of patients at risk of developing recurrence during that time interval.

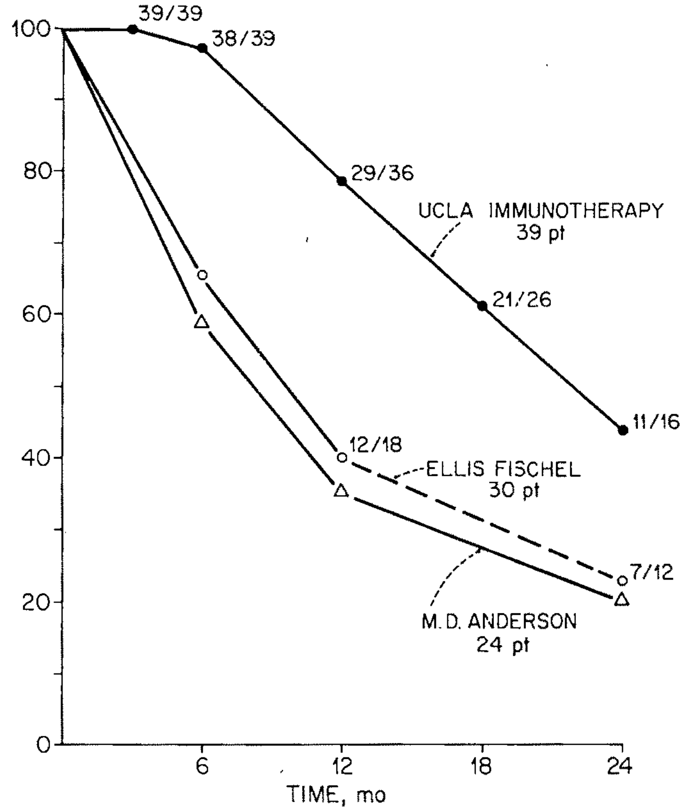

FIG. 2. Survival Rate: Stage III Melanoma. Percentage of patients surviving after surgical resection of all gross disease and postoperative adjuvant immunotherapy. Numbers separated by a slash (/) indicate number of patients surviving/number of patients at risk of dying during that time interval.

adjunctive immunotherapy with BCG alone or mixed with autologous irradiated tumor cells or allogeneic melanoma cells from tissue cultures.

Thirty-nine patients have been treated in this manner to the present time. The results summarized in Figs. 1, 2 compare the proportion of patients free of disease and their survival rates to a similar group of patients reported from M.D. Anderson Hospital.[3] Although this comparison may be questioned, the results of such treatment in patients with Stage III disease are surprisingly good. Almost 40% of these patients will remain free of disease at 2 years.

Similarly, the survival rates in this group of Stage III melanoma patients who received immunotherapy are higher on the curve at all points than those in other series.[5] It is obvious that the majority of these patients were followed for less than 2 years and therefore no statistical analysis of survival rates can be made. Furthermore, the use of historical controls for survival may become invalid because the improvements in chemotherapy may prolong survival in patients with recurrent disease. Nevertheless, the fact that the life table curve for both recurrence and survival remains higher at every point in time in immunotherapy patients would suggest the possible therapeutic benefit of adjunctive immunotherapy in these patients.

When the different immunotherapy groups were analyzed, no differences were noted between those who received BCG alone or BCG in tumor cell vaccine. However, the number of patients treated with allogeneic tumor cell vaccine was small when compared to the total number of patients treated. Therefore it is not possible at this time to state definitely whether the addition of allogeneic melanoma cells to BCG alters either the recurrence rate or the survival rate when compared to treatment with BCG alone.

BCG Immunotherapy as an Adjunct to Surgery in Patients with Stage II Malignant Melanoma

Having demonstrated the effectiveness of BCG immunotherapy in patients with advanced malignant melanoma, we began to investigate its possible usefulness as an adjunct to primary surgery for regional melanoma in 1970. Patients who had metastases to regional nodes were given immunotherapy with BCG alone or mixed with allogeneic melanoma cells following regional lymphadenectomy. This study began as a nonrandomized Phase I trial to determine if BCG could be administered in this manner with an acceptable toxicity and to look for evidence of therapeutic effect. The results are depicted in Fig. 3. The overall tumor free rate for the entire group of 67 patients is lower at all points in time when compared to 34 patients seen at UCLA during the same time interval who did not receive BCG immunotherapy. Although this was not a strictly randomized protocol, patients were not selected for immunotherapy on any basis except distance from UCLA and their willingness to participate in an investigational protocol. Note that the recurrence rate is also lower in the BCG immunotherapy group than is that of a comparable group of patients treated by surgery alone reported from the M. D. Anderson Hospital.[3]

Complications of BCG Immunotherapy:

We previously summarized the complications of BCG immunotherapy in cancer patients.[15] Nevertheless, these should be restated to emphasize the potential danger of this type of therapy. Intratumor injection with BCG frequently resulted in fever, chills, localized abscesses, and sinuses that drained for long periods of up to 3 months. Regional lyphadenitis was frequent. Occasionally a systemic infection occurred with associated granulomatous hepatitis. Although not observed in our series, fatal anaphylactoid reactions have been reported following repeated administrations of large doses of BCG vaccine. Because of these complications, we recommended much smaller doses of BCG for those patients who had been previously sensitized to BCG, or who were known to be tuberculin positive. Pretreatment with antihistamines and aspirin prior to and for several days following the intralesional injections appeared to decrease toxicity. Symptoms that persisted despite this regimen were treated with Isoniazid in a dose of 300 mg daily. Patients who had marked malaise and an influenza-like syndrome following BCG therapy generally responded promptly to Isoniazid administration. By careful adherence to these principles of management we did decrease toxicity following repeated intratumor injections of BCG.

In contrast to intratumor injections with BCG vaccine, the administration of BCG by the intradermal multiple puncture tine technique alone or of BCG mixed with tumor cell vaccine was usually tolerated very well with low incidence of hepatic dysfunction and only mild fever and malaise for short periods following vaccination. No instances of anaphylactoid reactions or marked toxicity have been associated with this method of administration. Some patients, however, developed hyperplasia of the regional lymph nodes draining the vaccination sites that did require biopsy to differentiate the hyperplasia from metastatic melanoma.

Discussion

The results of BCG immunotherapy in patients in advanced stages of malignant melanoma are encouraging. Direct injection of BCG into intradermal metastasis of malignant melanoma appears to be a highly effective means of therapy. Ninety per cent of directly injected lesions were destroyed and 17% of the patients treated had regression of uninjected nodules. This phenomenon was observed in patients with both regional and disseminated malignant melanomas. The fact that 31% of the patients remained free of recurrence for periods up to 6 years following initiation of immunotherapy is encouraging. These results indicate that there is not only a local effect with direct BCG injection into intracutaneous nodules but that in some patients a systemic effect is also achieved.

Patients with subcutaneous or visceral metastasis did not respond as well as those with intradermal metastasis. Temporary regression was noted in only 31% of the subcutaneous metastases injected with BCG and all patients subsequently developed progressive disease. Rarely was there evidence of regression of uninjected or grossly visible visceral metastases in these patients. In general, patients with large bulky lesions or visceral metastasis did not benefit significantly from the BCG immunotherapy alone. These disappointing results in this group of patients was noted early in our experience and more recently we have placed these patients on BCG immunotherapy following palliative surgical therapy to reduce tumor burden.

The explanation for the differences in response between these two types of patients is not completely clear at the present time. There are several possibilities that deserve consideration, however. First, there may be some basic biological differences between the behavior of malignant melanoma metastatic to skin and that involving the visceral organs, because it has been observed that response to chemotherapy is frequently better in patients with intradermal disease. However, these differences may be more quantitative than qualitative because patients who present with intracutaneous disease almost invariably develop visceral metastases within the first year and eventually die of their disease. Thus, almost all of those patients with intradermal metastases who were treated with immunotherapy probably had microscopic sub-clinical metastatic lesions in their lungs and liver, not clinically detectable at the time of initial presentation, which then regressed following intratumoral injections of BCG into their intracutaneous metastases.

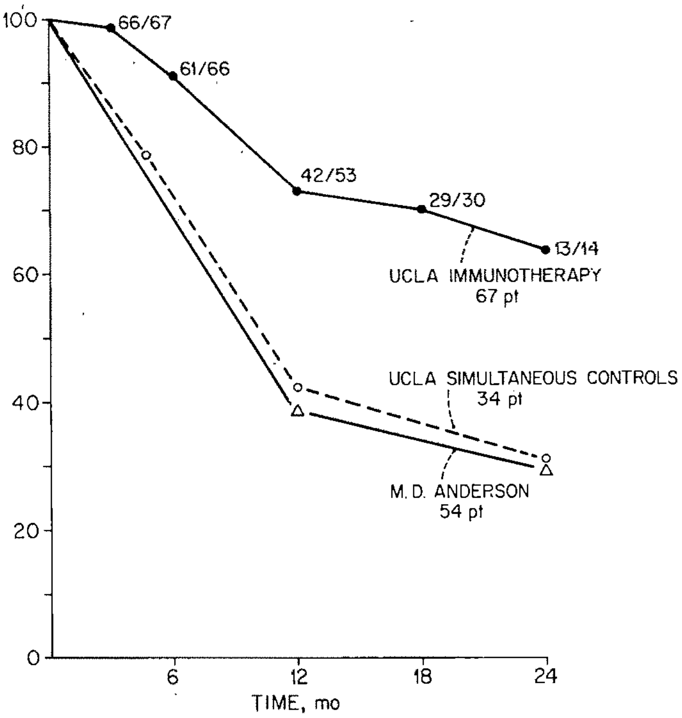

FIG. 3. Recurrence Rate: Stage II Melanoma. Percentage of patients free of recurrent melanoma following regional lymphadenectomy alone or lymphadenectomy with postoperative immunotherapy. Numbers separated by a slash (/) indicate number of patients who remained free of disease/number of patients at risk of developing recurrence during that time interval.

Another possible explanation for the differences in response rate between these two types of patients may relate to the immunocompetence of the host, since patients who are immunocompetent as judged by their ability to be sensitized to DNCB generally are more likely to respond to intratumor administration of BCG. There is increasing evidence that lack of immunocompetence in melanoma patients is primarily a manifestation of tumor burden. This is compatible with the observation that the patients who are most frequently anergic as judged by the hypersensitivity parameters are those who have visceral and subcutaneous metastatic lesions. Therefore it it not surprising that these patients would not respond as well to intratumor injections of BCG vaccine.

The correlation of nonspecific immunocompetence to tumor regression offers a clue to the mechanism of tumor regression in these patients. It would appear that BCG had no direct antitumor effect since it did not cause tumor regression in patients who remained tuberculin negative following BCG therapy. However, those patients who became tuberculin positive following BCG therapy usually had regression of their melanoma nodules following direct injection. This suggests that the antitumor effect was nonspecific and resulted from the induction of a delayed hypersensitivity reaction within the melanoma nodule. It is possible that the melanoma cells were destroyed by the immunologic reaction against the BCG associated-antigens as a result of an intense infiltration by lymphocytes and monocytes.

It is our opinion that intralesional BCG immunotherapy is the treatment of choice for patients with metastatic malignant melanoma limited to the skin. Up to 36% of these patients will have their disease controlled by this therapy alone with much less toxicity than that associated with chemotherapy or regional perfusion for extremity lesions. Although heat perfusion for extremity melanomas may be equally effective we reserve it for patients who fail to respond to intralesional BCG. Chemotherapy with imidazole carboximide alone or in combination with other chemotherapeutic agents has not had nearly the quality or frequency of complete responses that we have seen with intralesional BCG in this group of patients.

Our attempt to improve the effectiveness of systemic BCG immunotherapy in Stage III melanoma patients with visceral metastasis and large bulky subcutaneous metastasis by lowering tumor burden with surgical resection followed by adjuvant immunotherapy with BCG alone, or BCG and autologous or allogeneic tumor cell vaccine have been only partially effective. Clearly, some patients have benefited from this therapy program but most patients have proceeded to recurrence and death. As a result, we believe that these patients should be managed by a combination of surgery to reduce tumor burden, chemotherapy to further lower tumor burden and adjuvant immunotherapy to maintain remission. Hopefully, this new combined modality approach will be more effective than the use of any single modality alone.

The most exciting area for future development concerns the possible application of BCG immunotherapy as an adjunct to the definitive surgical treatment of patients with Stage II malignant melanoma and a poor prognosis because of metastasis to the regional nodes. The natural history of this disease is such that despite the surgical removal of all gross metastatic disease in the regional nodes, 60 to 70% of these patients develop recurrence within 2 years. Thus, patients with malignant melanoma and regional metastasis, in the majority of cases, have a local and regional manifestation of a systemic illness. Therefore, these patients are an ideal group in which to test the effectiveness of post-surgical immunotherapy based upon the principles of immune destruction of a limited number of sub-clinical metastases.

Our early results using BCG immunotherapy as an adjunct to primary surgical therapy are most encouraging and support the logic of this principle. Our results and those of others[3] suggest that the recurrence rate is less and the survival rate greater for patients with Stage II melanoma treated with adjunctive BCG immunotherapy. The preliminary nature of these findings, however, must be stressed since the duration of followup evaluation of these patients is not long enough to make a definitive statistical statement concerning its effectiveness. Additionally, it must be pointed out that these patients were not chosen at random and therefore it is possible that an unknown bias was introduced into their selection which may have influenced the results. With present knowledge, however, it does appear that BCG immunotherapy may be complementary to surgery but only continued followup of these patients can resolve this hypothesis. We are now randomizing patients into properly stratified and prospective clinical trials to compare no additional therapy after surgery with postoperative adjuvant immunotherapy using BCG alone or BCG with allogeneic tumor cell vaccine.

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Discussion

Dr. Thomas C. Moore (Torrance, California): I share with many of my transplant colleagues an unhappy feeling that we at times have a green thumb when it comes to rejection, and rejection is precisely what the tumor immunotherapists are trying to produce.

Accordingly, I would like to comment briefly on a possible mode of action of BCG and chemically similar tuberculoproteins.

It is probable, as Dr. Morton suggests, that their action is both central with respect to the lymphoid system and peripheral with respect to the tumor target mass site, and may well be related to the actions of potent vasoactive effector molecules.

Graham and Schild have found a tenfold increase in the activity of histidine decarboxylase, the histamine forming enzyme, at the site of the tuberculin reaction, and Schayer has reported an eightfold increase in histidine decarboxylase activity of lymphoid tissue following subcutaneous administration of complete Freund's adjuvant, also a tuberculoprotein.

We have found a 29-fold increase in allograft and an 8-fold increase in splenic histidine decarboxylase following renal allografting in rats. With Dr. B. M. Jaffe, of St. Louis, we recently have observed an increase in allograft and lymphoid tissue prostaglandin E series activity following rat heart allografting.

We also have encountered an increase in plasma activity of kallikrein, the bradykinin forming enzyme, following renal allografting in rats.

At this point it is of importance to note that histamine, bradykinin and prostaglandin of the E series may release, and be released by, one another.

(Slide) In a current study with L. Koppelmann, a UCLA Ph.D. candidate in experimental pathology working full time in my research laboratory—and, incidentally, referred to us by Dr. Morton—we have investigated the effects of repeated intratumor injections of bradykinin, a possible BCG effector molecule, on the growth of transplanted syngenic SV-40 virus induced tumors in hamsters and on the host splenic histidine decarboxylase activity of these animals. Injections were initiated when the tumors were 10 mm in diameter, after approximately five weeks of growth. Injections were made daily for four days, and on days 5, 7, 10, 14, 18 and 21. Bradykinin injected tumors' growth was slowed in comparison with saline injections, as the slide shows, and the response was dose-related, 50 mcg of bradykinin producing a less profound effect than the 250 mcg injection dose.

Bradykinin injections of tumor increased those splenic histidine decarboxylase, also in a dose-related way, and was correlated with reduction of tumor growth, as this slide demonstrates.

Injected tumors 14 days after initiation of injections showed histologic evidence of tumor destruction and massive filtration with mononuclear cells, in comparison with saline injected tumors which showed essentially no mononuclear cellular invasion. The saline injections are on the left-handed side, and on the right you see the bradykinin injected tumors at 14 days.

When two tumors were present and only one was injected, the growth of the noninjected tumor was slowed somewhat. It also was massively infiltrated with mononuclear cells similar to those found in the injected tumors, as shown on the right-hand side of this slide.

The actions of these vasoactive substances on tumor growth may in part be due to their action on cellular cyclic AMP activity. Cancer cells are known to have abnormally low cyclic AMP activity, and dibutryl cyclic AMP, a long-acting synthetic cyclic AMP analog, is known to slow tumor growth, both in vivo and in vitro.

I would like to suggest to Dr. Morton and others working in this field that bradykinin and possibly other vasoactive substances, such as histamine and prostaglandins of the E series, may be of value in the clinical management of malignant melanoma, particularly in the therapy of those anergic patients who are unable to mount an immunoinflammatory response to BCG or DNCB.

Dr. Edward T. Krementz (New Orleans): We at Tulane have also been interested in melanoma for many years, and look to Dr. Morton's work for aid and guidance.

I would, with tongue in cheek, take exception to the statement in Dr. Morton's abstract that the concepts of treatment of melanoma have not changed for the last 30 years, and continue to produce poor survival rates. In 1957, the late Dr. Oscar Creech, Dr. Bob Ryan and I introduced the treatment of melanoma with chemotherapy by perfusion which improved the survival rates for melanoma of the extremities.

(Slide) These are our direct survival rates at 5, 10, and 14 years, for stage I and stage II melanoma of the extremities, treated by perfusion with phenylalanine mustard, wide excision and skin graft, and usually, regional node dissection. As you will note, the per cent of patients free of disease with clinical stage I at five years is 80%, 76% at ten years, and 57% at 15 years. With stage II disease, the figures are 38, 32, and 23% respectively.

(Slide) We have recently constructed life tables (accumulated survival tables) and you can see, in stage I disease we have almost 80% survival extending out to 15 years. In stage II disease the survival is over 30% at 15 years.

(Slide) The best results occur in melanoma in clinical stage I melanoma of the upper extremities, and in women the salvage rates of over 80% are obtained at five years. I wish to emphasize these are patients with invasive melanoma according to review of the sections by our pathologists and include patients with dermal invasion of levels 3, 4, and 5 according to the Clark-McGovern terminology.

(Slide) The next slide shows the salvage rate of patients with satellitosis of the extremities. There were 45 patients treated from 5–15 years; 27 with negative nodes and 18 with positive nodes. Of the 27 with negative nodes, six remain free of disease for 5–15 years; of 18 with positive nodes, 5 remain free of disease. An additional 12 patients were controlled from one to four years.

BCG is an important additional modality to the treatment of melanoma. I believe its most important place will be in the treatment of stage II disease, particularly in men with multiple nodes who handle the disease poorly. We have also been using either BCG or some other type of immune therapy in this group of patients. We have one patient who failed to respond to perfusion who now is disease free for almost four years following injection of satellites with BCG similar to the method described by Dr. Morton.

One of the problems that should be emphasized is the toxicity, morbidity, and mortality occurring with BCG. There have been at least two deaths reported from the use of BCG in patients with malignancy and low resistance to infection, and by word of mouth, an additional two or more that haven't been reported as yet.

We had eight patients who had to be hospitalized following the use of BCG until we learned not to use the Tice strain of BCG intralesionally. I would like to know the type and dose of BCG that Dr. Morton uses, and whether he has had any toxicity from its use.

Professor Maurice Rossie Ewing (Melbourne, Australia): I believe it might be relevant to raise the question of the importance of the anatomical disposition of the disease, whether one is an advocate of immunotherapy or of chemotherapy.

We are all familiar with the favorable course that the disease often runs when it's confined to the skin of one extremity. I believe it's very important in discussing the place of any modality of therapy that we should take note of the anatomical disposition of the disease.

Dr. Joseph G. Fortner (New York, New York): We have a similar program under way at Memorial-Sloan Kettering Cancer Center. This is one of several programs designed, carried out and evaluated by a Melanoma Treatment Planning Team.

The group is multidisclipinary, with Dr. Carl Pinsky and Dr. Herbert Oettgen being the immunotherapists. I am the surgical representative and chairman of the group.

Our results with BCG are similar to those described by Dr. Morton, but our response rate is not quite so high. Dr. Pinsky tells me that in the Memorial series, 55 patients with surgically unresectable melanoma have been treated by BCG inoculation of their tumors. Nineteen had complete regression of all injected nodules. Five patients could not be evaluated, for various reasons.

This 38% regression rate in 50 patients occurred only where the melanoma was confined to skin and lymph nodes, and when the patient was immunologically competent. There was no regression of metastasis in vital organs, such as liver or lung.

In such patients, skin nodules responded somewhat poorly on injection; this in spite of a surprisingly high rate of DNCB reactivity in melanoma patients, even though disseminated disease may be present.

Most intriguing are the results in 30 patients in whom only some of the tumor nodules were injected. Two of these have regression of all disease, including noninjected nodules. They remain clinically free of disease, one more than two years, and one more than three years later.

In a separate study we are evaluating the adjuvant effects of BCG inoculation in melanoma patients who historically are at high risk of recurrence, but who are clinically free of disease following surgery. The tine technique is used, and the source for BCG is the same as that which Dr. Morton uses.

The program involves weekly injections for the first year, every other week for the second year, and then monthly in the third year.

Stage I melanoma is so successfully treated by surgery alone that meaningful data on adjuvant therapy from this group is difficult to obtain. They are not used in our study. Stage II patients, or those in whom the melanoma is clinically confined to regional lymph nodes, appear to be an ideal group for this evaluation. In a recent review at Memorial Hospital, we found that our five-year cure rate for stage II melanoma with surgery alone was 30% of 100 patients. Results here are sufficiently poor to obtain meaningful data in a reasonable period of time utilizing a practical number of patients. Our study requires only 48 randomized patients. We have avoided stage III patients since the amount of tumor may be prohibitive for beneficial effect by current immunological methods.

Our study has been under way only one and a half years. At this time ten of 20 patients receiving BCG have recurred, and six of 19 uninjected controls have recurred. The time for recurrence in the BCG-treated group is longer than the controls. These data are very preliminary and we must complete the study before drawing definite conclusions.

The importance of Dr. Morton's work is not only in his excellent results, but that it points a way for future productive investigation.

Dr. Anthony P. Monaco (Boston): I would like to comment with regard to the effectiveness of injection into the skin and the vulnerability of skin metastases.

Several years ago, when I started in immunology, Dr. Coons taught me that the best way to immunize a rabbit was to incorporate an antigen in an inflammatory focus, usually adjuvant, directly injected into the skin, and almost invariably in the skin where it is drained by a regional node. Thus, injection of rabbit foot pads or skin of the feet and legs usually gave the best response.

Furthermore, we know in animals that the best way to elicit the expression of a delayed response is by placing antigen in the skin. Therefore, this could also explain why the skin nodules that aren't injected are so vulnerable to the enhanced immunity, and therefore regress.

Secondly, I would like to say that Dr. Krementz' work might in fact be essentially the kind of work that Dr. Morton has been doing. When Dr. Gerry Austen and I were perfusing limbs for melanoma, one of the things that I remember very well was the fact that the nodules of the skin necrosed in a very profound inflammatory way, much like what would happen if you injected them with adjuvant. So perhaps the destruction of these skin nodules by perfusion with drugs set up the inflammatory focus, and this worked to encourage or facilitate the immunizing mechanism.

And then, thirdly, I would like to ask Dr. Morton a very important question. As transplanters, we try to enhance the formation of so-called enhancing antibody—antibody which facilitates the survival of the graft, rather than destroying it. As you know, enhancing antibody was first discovered by Kaliss in tumor graft systems. Every time we do this in studying adjuvants, we usually get the opposite effect; namely, accelerated rejection of our graft—which is what, obviously, would be good for a melanoma nodule. On the other hand, occasionally we get enhancement of the graft, which would be exacerbation of melanoma growth. So I would like to ask Dr. Morton: Does he ever make the melanoma grow more fast, rather than slower?

Dr. Donald L. Morton (Closing discussion): Dr. Moore, I think your work with vasoactive substances is very exciting, and I'm happy you are going to continue this work in other tumor host systems.

Dr. Krementz, I must apologize. I really didn't mean to shortchange the role of perfusion. That first sentence in our abstract should have been: "There have been no significant advances in the *surgical* treatment of malignant melanoma." However, now that you have raised the problem, I will mention that you are dealing with extremity melanoma in your perfusions, and as Professor Ewing has pointed out, extremity melanoma usually carries a more favorable prognosis than melanoma on the trunk. As I recall your slides, 37.5% of your patients given perfusion who had Stage II disease were alive and well for five years. I doubt if this is statistically significantly different from results from other Centers, doing just node dissection alone for Stage II melanoma; therefore, at least in my view, the role of adjuvant perfusion for Stage II melanoma still must be questioned. However, I certainly agree that for intracutaneous disease in extremities it is very useful and we use it if BCG doesn't work.

Dr. Fortner, I'm pleased to hear that the experience at Memorial with BCG immunotherapy has been similar to our own.

Dr. Monaco has raised a very interesting point as to why disease in the skin regresses and that elsewhere doesn't. I agree with him. I think it does have something to do with the rich lymphatics of the skin.

I am pleased that Dr. Monaco has brought up the question of enhancement following immunotherapy. It has been clearly demonstrated in experimental animals that enhancement of tumor growths or prolonged survival of organ allografts can be achieved in animals by active immunization with allograft antigens or passive transfer of enhancing antibodies to allograft antigens. However, the experimental conditions under which this enhancement can be produced are very specific in terms of the temporal relationship between transfer of the enhancing antibody and transplantation of the tumor or organ allograft. Enhancement is only seen if these immunologic maneuvers are performed prior to or within a few days of the time of tumor transplantation. If the immunologic maneuvers to achieve enhancement are delayed one week or more, enhancement is not achieved and in fact the tumor or organ grafts are rejected in a normal manner. In other words, once cell mediated immunity has been turned on for at least one week, it is generally not possible to achieve immunologic prolongation of tumor or organ allograft survival.

We have been able to produce enhancement of tumor growth with BCG in experimental animals but the conditions under which this is achieved are very similar to conditions under which enhancement is produced in the tumor homograft situation. That is, the animal has never been exposed to the tumor before and the BCG is given in large doses at the same time as the tumor is transplanted. One can get enhancement of tumor growth in some tumor host systems using these experimental conditions. However, this is quite a different phenomenon from what one sees in man with a malignancy, because most human neoplasms have been *in situ* for long periods of time (1–10 years) and cancer patients already have an on going immune response against the tumor antigens in their neoplasms. Thus, it would be difficult or impossible to produce classical enhancement in this situation. Perhaps that is why we have not seen any clear cut instance of enhancement following BCG immunotherapy.

So I think that, although we talk about these things as being similar, the time course of the situation makes them different.

Major Hepatic Resection Using Vascular Isolation and Hypothermic Perfusion

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The technique and results of 29 major hepatic resections using the method of complete vascular isolation and hypothermic perfusion of the liver are reported. The method enables the surgeon to perform otherwise difficult or impossible resections through chilled bloodless hepatic parenchyma. Major intrahepatic vascular structures can thus be recognized and controlled readily under clear vision. Direct neoplastic involvement of, or tumor thrombi in the portal vein, hepatic vein or vena cava, can be successfully dealt with by appropriate surgical measures. The operative mortality was 10.3% for this series which included many tumors previously deemed unresectable. The technical detail and intraoperative physiologic monitoring crucial to success in the use of the method are described. It is hoped that with the widened scope of resectability afforded by this technique, and the use of adjuvant chemotherapy, the currently experienced low cure rates for hepatic cancer can be improved.

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MAJOR HEPATIC RESECTION for a neoplasm can tax the skill and judgement of even the most experienced surgical team. The tumor may be close to main hepatic veins, extend into the adjacent lobe, or be intimately attached to the inferior vena cava or portal vein. Adjacent viscera, the diaphragm, or abdominal wall may be involved. Removal of even a peripherally located tumor can invoke problems with vascular control, biliary drainage and with the remaining lobe's transected raw surface. Because of these difficulties, prohibitively high operative mortality rates have previously been recorded.[1,9]

In an effort to deal more adequately with these problems, a new method of hepatic resection was devised, and has been used at Memorial Sloan-Kettering Cancer Center by the authors[8] since 1970. *In vivo* isolation and chilling of the liver by an asanguinous perfusate is carried out. Accurate, unhurried transection of liver parenchyma is then possible, decreasing the risk of technical error, bile fistula and intraoperative hemorrhage. With judicious physiological monitoring, complete clamping of the inferior vena cava and portal vein without use of bypass shunts has been well tolerated for more than two hours. Functional recovery of the cold perfused liver has been rapid as judged by serial 99m Technetium scans, biochemical tests and patient well being. In an effort to further improve cure rates, multiple drug chemotherapy is given after recovery from the surgery. This is usually by combined intrahepatic arterial infusion and systemic administration. This program has increased the resectability rate of hepatic neoplasms, decreased the mortality rate, and appears to be improving patient survival.

Materials and Methods

Technique

Abdominal exploration is carried out through a subcostal incision. If the lesion is resectable, the incision is lengthened bilaterally and extended through a convenient intercostal space, usually the seventh. The diaphragm is incised radially toward the vena cava. The liver is completely mobilized except for major vasculature and the common bile duct. The round ligament is divided and the falciform ligament incised to the vena cava. Retraction of the liver is upward and to the left so that peritoneal reflections to the right lobe of the liver can be incised. Retraction and dissection are con-

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Presented at the Annual Meeting of the American Surgical Association, Colorado Springs, Colorado, May 1–3, 1974.

tinued so as to expose the right kidney, adrenal gland, and vena cava. The right adrenal vein is then doubly ligated, divided and the dissection continued behind the vena cava. This is continued until the vena cava is completely free posteriorly from the diaphragm to just above the right renal vein. Usually, one or two vertebral veins must be dealt with as they enter the posterior aspect of the vena cava. The right lobe of the liver is then returned to its fossa. With large tumors, some decrease in size of the lobe can be achieved by preliminary ligation of the hepatic arterial and portal venous branches. Difficulties in mobilization are thereby lessened in many instances.

Peritoneal attachments of the left lobe to the diaphragm are incised; the triangular ligament cut and ligated. The lesser omentum is severed; posterior peritoneal reflections onto the vena cava are cut and the left side of the liver mobilized. An accessory hepatic branch from the left gastric artery is commonly encountered. If present, it is isolated and preserved. At this time, the surgeon's hand can be passed freely beneath the liver and vena cava from the diaphragm to the renal veins. The liver is then retracted upward for dissection of the porta hepatis. The celiac axis, hepatic artery and gastroduodenal artery must be isolated. The portal vein and common bile ducts are isolated and all lymphatic and areolar tissue in the porta hepatis divided between ligatures.

Isolation of the liver being completed (Fig. 1), the gastroduodenal artery is cannulated using a silastic catheter (internal diameter 1.1 mm, external diameter 2.7 mm). The portal vein is cannulated either via a venotomy or via the branch of the lobe which is to be resected. These cannulae are kept patent with a slow infusion of Ringer's lactate at room temperature. The common bile duct is then occluded with a small Pott's clamp. The liver is then ready for hypothermic perfusion. The common hepatic artery and portal vein are clamped proximal to the cannulae (Fig. 2). The infrahepatic vena cava and suprahepatic vena cava are separately occluded by vascular clamps and a cavotomy is made immediately inferior to the liver for placement of a #32 French catheter to drain the perfusate. Ringer's lactate solution, chilled to 4 C and with 5 mg/l heparin, is used. This solution passes through coiled tubing immersed in ice, to the hepatic artery and portal vein, and after traversing the liver, exits through the hepatic veins into the vena cava. After obtaining adequate chilling of the liver parenchyma and checking for complete vascular isolation, the liver is ready for asanguinous resection.

The liver's capsule is incised at an anatomical location dictated by the tumor, and the extent of the indicated resection. Liver parenchyma is transected using the scalpel's handle (Fig. 3). Blood vessels and major bile ducts are readily identified and individually occluded with silver clips or catgut ligatures. Transection of the liver is carried out in a concave plane, fashioning anterior and posterior flaps to facilitate approximation of the raw transection area with interlocking #1 chromic catgut stitches (Figs. 4, 5). The lobar artery, portal vein and hepatic duct of the resected lobe are individually ligated and divided at the liver hilum. Finally, the appropriate major and minor hepatic veins are severed as the plane of transection is carried towards the inferior vena cava. After removal of the transected lobe, the resection edge is checked for leakage of perfusate which would indicate bleeding sites when hepatic circulation is re-established. This completed, the cavotomy is closed and blood flow re-established through

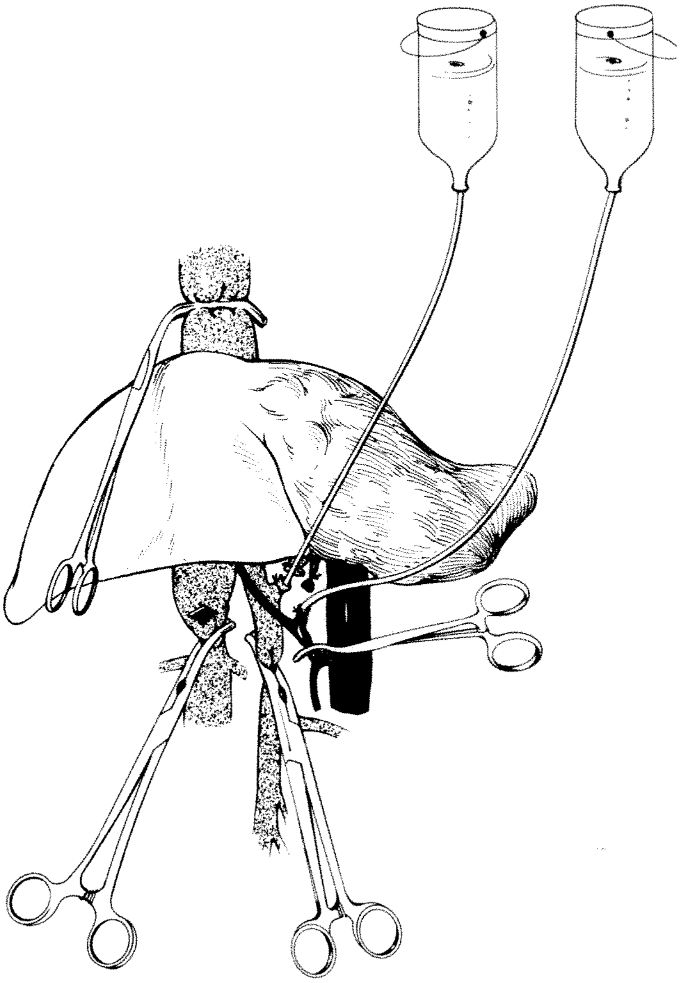
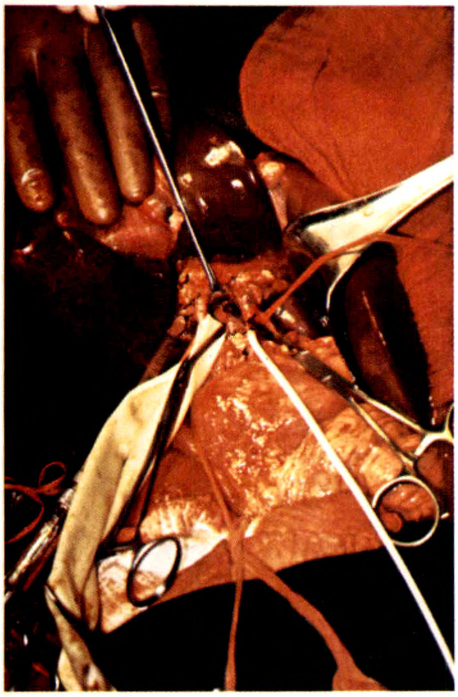
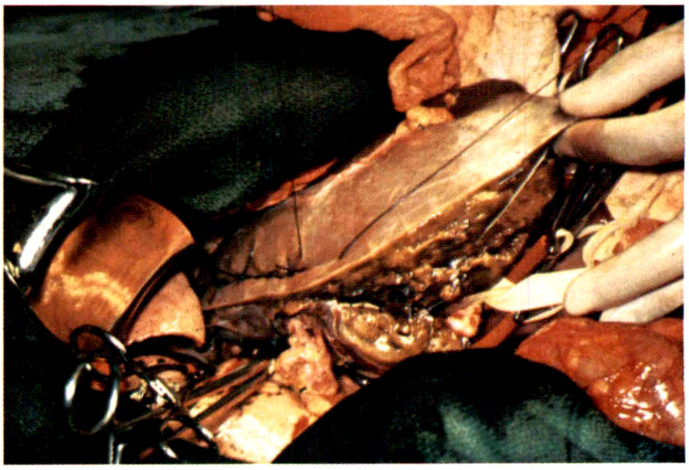
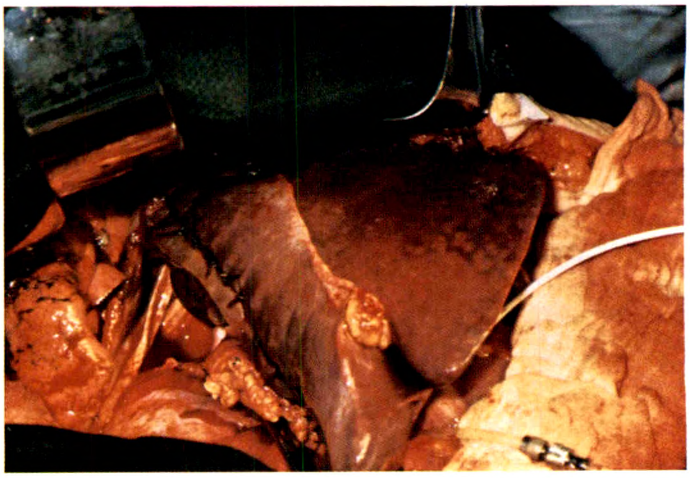
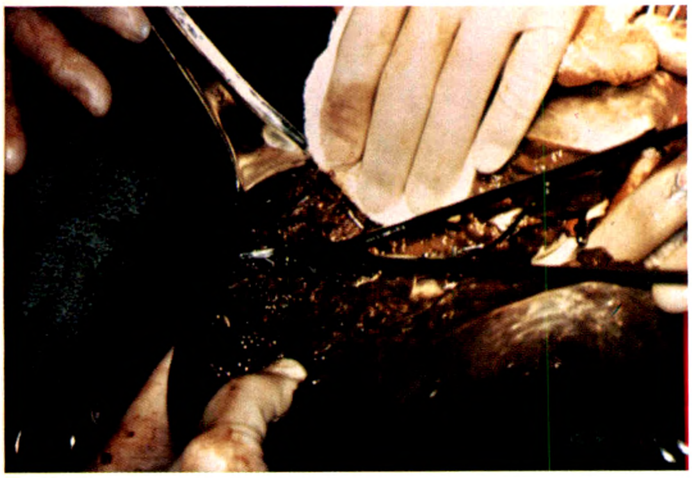


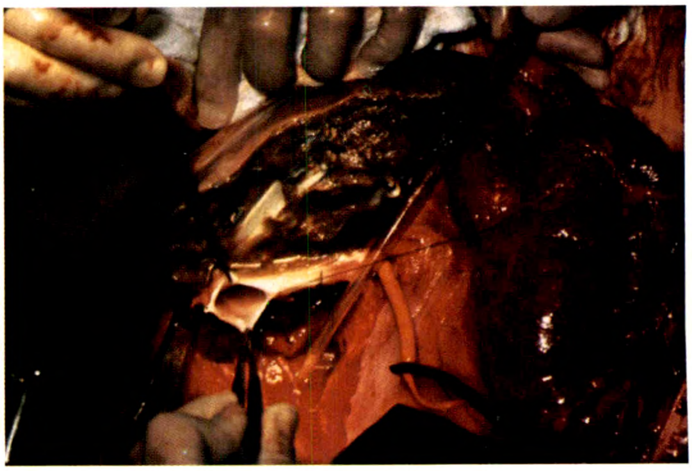
FIG. 1. Isolation perfusion technique prior to left hepatic lobectomy. Catheters placed in portal vein and hepatic artery for cold perfusion of right lobe. Arterial catheter can be placed via the gastroduodenal artery. Occluding clamps applied to common hepatic artery, portal vein, suprahepatic vena cava, and infrahepatic vena cava. Note cavotomy just above lower clamp for egress of perfusate. Catheter is placed here to collect perfusate.

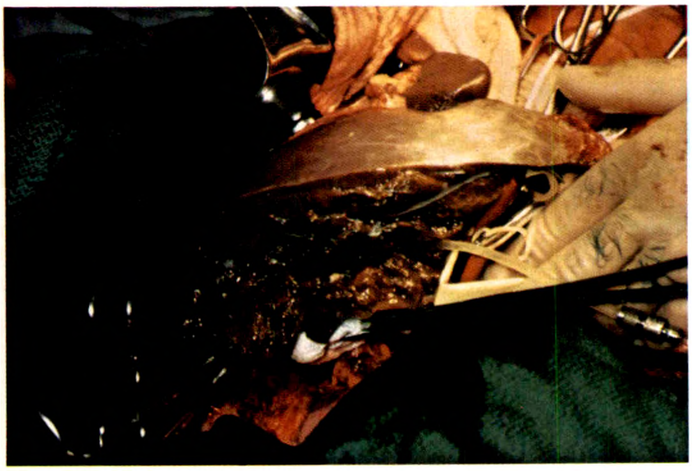












the vena cava. The cannula is removed from the portal vein and blood flow re-established. Occlusion of the hepatic artery is released but the catheter in the gastroduodenal artery remains for subsequent chemotherapy administration.

Intraoperative Monitoring

Maintenance of blood volume, hemodynamic state and acid-base balance require careful monitoring. An electrocardioscope, esophageal thermocouple, arterial lines, central venous catheter, and a urinary catheter are routinely used. Serial microhematocrits and thromboelastograms are carried out every hour.

Clinical Material

Table 1 indicates that 141 patients had major hepatic surgery at Memorial Sloan-Kettering Cancer Center by the authors during the period of this study.[6–8] Forty of these patients underwent major hepatic resections with 29 being carried out using the isolation perfusion technique. They have been studied postoperatively by serial ^{99m}Tc liver scan, biochemical tests and in many cases, postoperative arteriograms. The experience with this group of patients forms the basis of this report.

Adjuvant Chemotherapy

Four drugs are given when the patient has recovered from surgery. Actinomycin-D at a dosage of 20 g/kg is given as a single weekly bolus through the hepatic artery catheter. Methotrexate 8.25 mg/kg is dissolved in 30 cc of saline and given by constant infusion over seven day periods via a Sigmamotor pump. Heparin is added to maintain patency of the catheter. Systemically, 5-fluorouracil is given intravenously in a dosage of 10 mg/kg body weight once weekly. Cyclophosphamide is taken orally daily in a dosage of mg/kg. This program is maintained for one year if tolerated by the patient and there is no sign of activation of the cancer.

Results

Twenty-nine patients had a major hepatic resection using the *in vivo* liver isolation and cold perfusion technique. Ischemic times of the liver (Table 2) ranged up to two hours and 14 minutes. Perfusion was through both the hepatic artery and portal vein in 20 patients, portal vein only in six, and hepatic artery only in three. Choice of infusion site was arbitrary initially, but it became evident that optimal preservation was achieved by perfusing both the hepatic artery and portal vein. An average of eight liters of chilled Ringer's lactate was used for each patient.

Physiological Changes

The central venous pressure was deliberately raised to 10–15 mm of water in most patients by blood or plasma administration prior to liver isolation. This value was maintained during the period of isolation perfusion. No significant drop of the systemic arterial pressure was observed. A fall in body temperature often developed during liver isolation in the earlier patients and was attributable to leakage of chilled perfusate. Urine output was unchanged during the vena cava occlusion in most instances. In the event of any decrease, furosemide or mannitol was administered, with a prompt response in most instances.

A striking decrease in serum potassium was seen in nearly all patients in the early postoperative period (Fig. 7). Albumin levels were maintained, possibly because of generous intravenous administration in the first few days postoperatively. There was a transient decrease in serum globulin levels and a transient increase in alkaline phosphatase, bilirubin and glutamic oxaloacetic transaminase (SGOT). Bilirubin and SGOT values returned to normal, usually during the second postoperative week. The alkaline phosphatase levels usually remain elevated for three or more weeks. These biochemical changes are similar to those observed after hepatic resection without isolation perfusion of the liver.[11]

Operative Mortality

There was one operative death. This was in the first patient resected by this technique. Isolation of the liver was incomplete and blood leaked into the system. This

FIG. 2. (Left, top) The liver is retracted cephalad exposing the porta hepatis. Cannula is in gastroduodenal artery; common bile duct is occluded by a vascular clamp. A penrose drain protects the bile duct. The portal vein is cannulated through the right branch of portal vein. FIG. 3. (Left, center) The right lobe is being removed using finger fracture technique. Major vascular and biliary structures are occluded with silver clips. FIG. 4. (Left, bottom) The right lobe has been removed. The cut surface is concave so that a posterior lip can be used to close the bare surface. A clamp on the vena cava above the liver is shown to the left. FIG. 5. (Right, top) The bare area is being closed using the posterior lip. Interlocking chromic catgut sutures are used. The suprahepatic occluding clamp is to the left. FIG. 6. (Right, center) The resection has been completed. The catheter remains in the gastroduodenal artery for administration of chemotherapy after the patient recovers from surgery. FIG. 8. (Right, bottom) A right hepatic lobectomy has been performed. Tumor involvement of right hepatic vein and adjacent vena caval wall necessitated resection of adjacent portion of vena cava. The hepatic vein of the medial segment of the left lobe is seen above the vena cava. The suprahepatic vena caval occluding clamp is to the left.

TABLE 1. *Hepatic Surgery at Memorial Hospital (7/1/70–3/31/74)*

Procedure	No. of Patients
Resections (Total)	40
A. with isolation perfusion	(29)
B. without isolation perfusion	(11)
Hepatic, Portal Vein and Bile Duct Resection	5
Hepatic and Bile Duct Resection	2
In Vivo Extra Corporeal Chemotherapy Perfusion	3
Wedge Excisions	6
Excision Giant Cyst	2
Echinococcus Cyst	1
Liver Transplant (Total)	5
A. auxiliary	(3)
B. orthotopic	(2)
Hepatic Artery Ligations	55
Exploratory Laparotomy	22
Total	141
Resection Rate	34% (47/136)

resulted in hypovolemia, cardiac standstill and death. A second patient died from pulmonary embolism six hours after the operation. The source of the pulmonary embolus was apparently from the popliteal veins. Phlebothrombosis had developed after a gallbladder operation some three weeks previously. The third patient died of hepatorenal syndrome about four weeks after surgery. This patient had a peculiar generalized granulomatous reaction in the lungs and peritoneal cavity associated with some hepatic fibrosis. This unclassified condition appears to have been an important factor in the result which is otherwise a puzzle. The overall operative mortality rate for this series of 29 patients is thus 10.3%.

Complications

Complications are listed in Table 3. Subphrenic abscess and wound infection are the most prominent. This high and unacceptable incidence of subdiaphragmatic suppuration appears related to inadequate drainage of a large dead space left when large tumors are removed. Isolation of the liver leads to considerable lymphorrhea for the first few days postoperatively and this may be a contributing factor. One patient developed acute tubular necrosis secondary to a prolonged period of hypotension. Dialysis was necessary but recovery appears complete.

TABLE 2. *Hepatic Ischemic Time (Duration of Vascular Occlusion)*

Time (min)	Hepatic Artery	Portal Vein	Vena Cava
60	5	6	9
60–90	10	10	12
91–120	9	10	6
120	4	2	1
Range	48–147 min.	49–136 min.	45–133 min.
Mean	89 min.	85 min.	65 min.

* One intraoperative death.

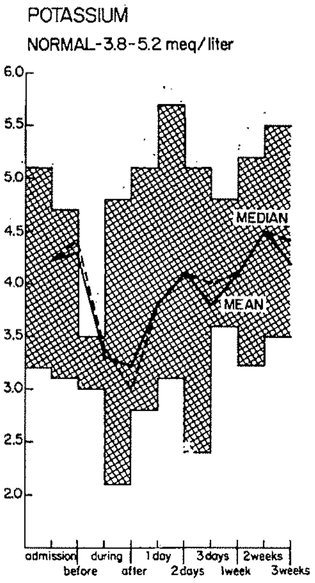


FIG. 7. Changes in serum potassium during and after hepatic resection with isolation and cold perfusion of the liver. Note hypokalemia in the immediate postoperative period.

Resectability Rate

The resectability rate in this series of patients during the period reported is 34%. Two patients had a simultaneous en bloc right nephrectomy. One had a simultaneous en bloc right hemicolectomy. Three patients had extended right hepatic lobectomies. Sixteen of the patients had primary liver cancer, and ten had metastatic cancer in the liver. Three patients had benign lesions. Fifteen patients had been explored elsewhere, many of whom were considered nonresectable.

Survival

Intermediate evaluation of treatment effectiveness for the 26 surviving patients reveals that good palliation and possible cure have been achieved for most. Excluding the three operative deaths mentioned above, three of 12 patients with primary liver cancer, and six of ten with metastatic cancer have died at various times during the three year period (Table 4). One patient with a rhabdomyosarcoma in the liver was resected less than three months ago and three patients with benign lesions are all alive: one at four months, one at 24 months, and one at 44 months. The results of resecting primary hepatomas is particularly gratifying. Nine of 12 patients who had resections are still alive although the period of followup only extends to 30 months. As expected, the results for metastatic cancer in the liver are not as good, but are still encouraging since two of five, or 40% are alive and well at two years.

Especially interesting are the results of resection in nine patients who had extensive hepatic disease. These neoplasms would have been non-resectable by the usual

TABLE 3. *Complications Following Liver Resection*

Complications	No. of Patients
Subphrenic Abscess	9
Wound Infection	9
GI Bleeding	3
Pleural Effusion	2
Serum Hepatitis	2
Brachial Plexus Palsy	2
Postoperative Bleeding	2
Renal Failure	2
Respiratory Failure	2
Intestinal Fistula	1
Intraoperative Bleeding	1
Convulsion & Mental Change (transient)	1

method of carrying out hepatic resection. Table 5 records the extent of tumor and the significant palliation achieved with long term survival in all but one patient. The survival times ranged 9–31 months with five of the nine patients currently alive and well. Three patients succumbed to disease from nine to 14 months after resection. One patient died of an inadequately drained subphrenic abscess five months after the operation.

Three patients had hepatic resections for hepatoma which had metastasized outside the liver. Two of the three are presently alive. One is living and perfectly well at 31 months. One is alive with disease at 24 months. One died of disease at nine months. Resection of metastatic tumor to the liver (Table 6) has not produced comparable results although excellent palliation has been achieved in some instances.

Discussion

In vivo isolation and asanguinous perfusion of the liver permits hepatic resection to be carried out under controlled conditions. Resection of major hepatic veins flush with the vena cava, removal of a portion of vena caval wall (Fig. 8), excision of neoplastic involvement of liver tissue adjacent to vena cava, as well as neoplastic thrombosis of the portal vein are examples of surgical problems that can be dealt with using this method. Although the technique is a direct outgrowth of experiences with total hepatectomy and orthotopic liver transplantation,[4,12] it has served to decrease the need for this procedure. At first, it was intended to remove the liver for resection or repair and then do an autotransplantation. There proved to be little need to remove the liver for all the required surgery could be done without transecting major blood vessels or the common bile duct. "Bench" surgery as for the kidney[2] is avoided, but the advantages of the isolation method are retained.

TABLE 4. *Survival Following Hepatic Resection with Isolation Perfusion*

Survival (months)	Primary	Metastatic
3	100% (12/12)	100% (10/10)
12	75% (6/8)	67% (4/5)
24	80% (4/5)	40% (2/5)
30	100% (2/2)	— (0/1)

3 patients with benign lesion alive at 4, 24, 44 months.
1 patient had resection less than 3 months.
3 postoperative deaths (2 primary, 1 metastatic).

TABLE 5. *Survival Following Hepatic Resection for Extensive Hepatic Disease*

Patient	Involvement	Followup
V.T.	Hepatic vein & IVC wall	18 (mos) NED
C.I.	M. Hepatic vein & IVC & margin of resection	9 (mos) DOD
R.S.†	Portal vein	10 (mos) DOD
V.O.†	Portal vein	9 (mos) NED
B.F.	Portal vein & margin of resection	5 (mos) DOCNED
B.B.*	Main hepatic vein & margin of resection	27 (mos) AWD
R.R.†	Margin of resection	24 (mos) AWD
I.P.	Other lobe	14 (mos) DOD
S.F.	Common hepatic duct & porta hepatic	31 (mos) AWD

NED = No evidence of disease.
DOD = Died of disease.
AWD = Alive with disease.
DOCNED = Died of other causes; no evidence of disease.

The method of *in vivo* isolation and perfusion of the liver can be used for short term perfusion with chemotherapeutic agents at high dosage levels.[3,10] This approach is applicable where the liver is involved at multiple sites with metastatic cancer and where there is little or no disease outside the liver. Advantage can be taken of the liver's dual blood supply. Hepatic arterial perfusion with oxygenated normothermic blood containing the chemotherapeutic agent, Actinomycin-D has been done to treat metastatic disease. Simultaneous perfusion through the portal vein with chilled perfusate

TABLE 6. *Hepatic Resection Done in Patients With Metastases*

Patient	Pathology	Site of Metastases	Status
B.F.	Carcinoid	Adrenal (right)	5 mos. DOC
B.B.	Colon CA	Pulmonary (sol)	8 mos. DOD
B.S.	Melanoma	Retroperitoneal, chest wall	4 mos. AWD
E.Q.	Melanoma	Small Intestine	19 mos. DOD
S.I.	Hepatoma	Porta Hepatis & supradiaphragmatic lymph node	31 mos. L/W
R.R.	Hepatoma	Celiac & Porta Hepatis & pulmonary	24 mos. AWD
G.I.	Hepatoma	Pulmonary (solitary)	9 mos. DOD

DOC = Died of other causes.
DOD = Died of disease.
AWD = Alive with disease.
L/W = Living and well.

can preserve liver cell function. This approach has been used in three patients with excellent results.

The intraoperative physiological effects of liver isolation are important. It is essential that the central venous pressure be moderately elevated prior to occluding the vena cava. Optimally, a central venous pressure of 10–15 cm of water is achieved before occlusion of the vena cava is carried out. Monitoring of urine output is of great importance and must be maintained throughout the procedure. The blood pressure may be temporarily decreased by about 20 mm of mercury after the initial occlusion of the vena cava, but this gradually returns to normal levels. The most prominent physiological abnormality is a decrease in serum potassium which is present in most patients in the early postoperative period. Levels of about 2 mEq/L are not uncommon if potassium has not been given prophylactically during the operative procedure. The cause of the hypokalemia has not been determined but is likely related to the type of perfusate which has been used. The best perfusate has not been determined although studies are in progress.

Perfusion of the liver appears to be optimally through both the hepatic artery and portal vein. Perfusion of the hepatic artery only was used in three patients and through the portal vein only in six patients. The impression was that the chilling of the liver and perfusion was less than optimal. In the event of need for prolonged isolation, inadequate chilling of the liver would occur with a single vessel perfusion. Perfusion through both vessels has permitted excellent liver function after about 5½ hours ischemic time under comparable conditions in a liver transplant patient. Function of the liver after isolation, perfusion and resection is well maintained with no obvious decrease in the liver's ability to regenerate. Serum bilirubin, SGOT and alkaline phosphatase levels have been comparable to those seen in patients who have not been subjected to isolation perfusion of the liver. Renal function has been compromised in two patients, but these are directly related to prolonged periods of hypotension and not to any apparent occlusion of the vena cava.

There have been no instances of bile fistula and a T-tube has not been used in any of the patients. Subphrenic abscess and wound infection remain unacceptably common. This appears related to the large raw surface which is developed secondary to the isolation of the liver and from the large size of many of the tumors removed. Inadequate drainage of the subphrenic area in such instances would appear to provide a perfect nidus for infection. Considerable attention is being directed toward solving this troublesome complication.

Survival of the 29 patients subjected to hepatic resection using the isolation perfusion technique is most encouraging. There was only one intraoperative death and this was due to inexperience with the technique. Two other deaths occurred in the early postoperative period and would appear secondary to pathological conditions not directly relatable to the isolation perfusion method. The 26 surviving patients have done remarkably well, particularly in view of the fact that the majority have extensive tumors, 15 having been explored elsewhere and mostly deemed non-resectable. Nine or about 30%, had extensive intrahepatic cancer, but even here, highly significant palliation and long term survival has been achieved for eight of the nine patients. Sufficient time has not elapsed for five year survival rates, but preliminary results give hope for an improved cure rate over that previously achieved. The place of adjuvant chemotherapy,[7] particularly administered intra-arterially as well as systemically after hepatic resection, remains to be determined. The effectiveness of combination drug chemotherapy[5] after hepatic artery ligation in patients who have nonresectable hepatoma is the basis for our hope that this drug regime will improve cure rates for patients who may have occult residual disease.

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DISCUSSION

Dr. William P. Longmire, Jr. (Los Angeles): This is an area in which we have been interested for a number of years. With Dr. Gerald Buckberg and Dr. William Joseph, we reported a number of years ago some basic physiologic studies on the liver with cold asanguinous isolation perfusion, but we have not utilized this technique clinically.

I'm very impressed with the cases Dr. Fortner has presented, and I'm sure that at least the series of eight cases, as he indicated, probably could not have been resected in any other manner. However, some of the other major hepatic resections, I think, could be done, and I assume that he would agree that this is not necessary for all types of major hepatic resections.

We reported a short time ago on a series of 125 cases seen at our hospital since 1955 with possible lesions that could be corrected surgically. Fifty-two patients with eight types of benign conditions underwent 34 hepatic resections. Only two deaths were reported within two months of the time of the operation, and both were associated with conditions occurring with extensive hepatic sepsis.

I would assume under conditions of this kind that such isolation would not be necessary, and we have found that the use of a rather simple liver clamp has allowed us to divide the parenchyma and to perform the correction and the closure of bile ducts and blood vessels, large veins, and so forth, deliberately, serving somewhat the same purpose as the isolation that Dr. Fortner and his group have used.

The operative mortality, however, of hepatic resections for primary malignant disease has been higher. Four deaths occurred in our series within two months after 30 resections. Nine of these patients were alive at the time of our review, five for more than four years after the resection.

Metastatic hepatic tumors were resected in 11 patients. One of those patients was alive 16 months after resection, and five had lived for more than one year.

I was under the impression that our results had been quite unsatisfactory with hepatic arterial infusion, and I was surprised, in reviewing these cases that had been treated with hepatic artery infusion with 5-fluorouracil, that we had had some rather surprisingly good results in a group of eight patients who had been found to have nonresectable tumors. The average survival time after recognition was 14½ months, and two of the patients were alive 4 and 2½ years after the diagnosis had been established.

In summary, I would like to indicate that I think that this technique that Dr. Fortner and his associates have described will be useful in extending hepatic resection in some of these cases, particularly in primary hepatic tumors with extensive involvement, but probably there are many other major hepatic resections in which the technique would not be necessary.

Dr. Elton Watkins, Jr. (Boston): I would like to pay particular attention to the metastatic colon lesions. I envy Doctor Fortner his material because in my first series of hepatic artery infusions in 145 patients, all of which were evaluated for curative resection, I found only two patients suitable for resection. This may reflect a characteristic of our particular service in receiving referrals of patients with disseminated disease.

Both resected cases were disasters from which we learned something. The first patient was a young man with a giant metastasis from colon malignancy in the right and middle lobes of the liver. Giant solitary metastases of this type are not suitable for infusion chemotherapy. There is too much tumor with central necrosis, and there is hazard of infection during infusion. If possible, they should be resected.

We did an 80% liver resection in the first patient and then thought that we would be clever and infuse 20% glucose and heparin solution into the hepatic artery to control postoperative hypoglycemia. The patient died after 8 days with thrombosis of the catheterized artery. Consequently, I would raise some question as to the safety of hepatic artery catheterization at the time of extensive resection.

The second patient was a man who underwent 60% resection for solitary giant metastasis from colon malignancy. Although the margins of resection were quite adequate, the patient died of abdominal carcinomatosis nine months after operation. This raised the question with us whether patients with highly vascular lesions should undergo a period of arterial infusion chemotherapy to reduce the growth potential of the metastasis prior to resection.

I would like to raise a point concerning survival. In Doctor Fortner's report, the survival after resection of colon metastases and infusion chemotherapy is 33% at 18 months. This figure is comparable to that for infusion chemotherapy alone without resection as shown in this modified actuarial survival curve (slide). However, I believe one can make a case for resection in this situation since the survival curve after infusion alone does not continue up to 40, 50, 60 months, but all patients are dead at the end of 36–37 months. Consequently, hepatic resection is desirable as a possible curative procedure. The complete mortality at 36 months after hepatic artery infusion chemotherapy is quite different from the situation in arterial infusion chemotherapy of head and neck tumors, where one can expect a low percentage of complete control of disease.

I would like to ask Doctor Fortner how he selects patients for resection of hepatic metastases from colon primaries. We have used arbitrary indications: solitary metastases, a patient young and strong enough to tolerate resection and derive benefit from it, and, finally, a delay of one year after removal of the primary tumor to permit development of occult metastases which might contraindicate resection of the solitary giant metastasis.

Dr. William V. McDermott, Jr. (Boston): In 1957, after an experimental series with Dr. Huggins and Dr. Carter, we introduced a technique of selective hypothermia of the liver in clinical hepatic resection. The technique we used at that time was carried out by introducing ice cold saline into the peritoneal cavity, with occlusion of the hepatic artery; after sufficient cooling of the liver, the portal vein was then occluded and resection carried out. A siliconized polyvinyl shunt between the mid-colic vein and an antecubital vein was utilized, with the thought at that time that we would prevent splanchnic pooling.

This went very well at the time, but, interestingly enough, in 40-odd cases since then we have not as yet encountered an instance where it seemed necessary or reasonable to carry out selective hypothermia. I think probably there are cases where, even with modern techniques, the addition of hypothermia will permit long periods of occlusion. In the instance I referred to, the occluded period was 53 minutes, and was tolerated very well, without any unusual sequelae in terms of hepatic dysfunction postoperatively.

However, since that time it's become increasingly apparent that the human liver will tolerate quite long periods of total inflow occlusion without hypothermia—certainly, 15 to 20 minutes at least—and that shunting is not necessary, as, actually, Gardner Child showed some years ago in man, in distinction to some other mammalian species. So, while admiring the technique and, certainly educated by the extraordinary series Dr. Fortner has presented to us, I wonder how often this technique is really applicable and necessary in major hepatic resection.

Dr. Joseph G. Fortner (Closing discussion): Drs. McDermott and Longmire both bring up an important point: When is it necessary to use this technique? Clearly, it's not necessary in all instances. I do use it for almost all major lobectomies for my life becomes much more relaxed and simple where everything is under control. The thought of transecting the liver, with the blood flowing and being unable to really define structures, just doesn't appeal to me. Once you get used to the controlled technique which I have described, I believe you will come to the same conclusion.

The hepatic artery ligation is an especially effective treatment for hepatoma in instances where these are not resectable, or the patient is not a candidate for transplantation. We are very impressed by results with hepatic ligation and infusion chemotherapy through an in-dwelling hepatic artery catheter. We have improved our results by using the 4-drug combination that I described, rather than just using 5-FU alone, and I recommend that to you.

Dr. Watkins has raised some other important points. Preoperative infusion of chemotherapy might have severe toxic effects which may be prolonged. Delay in surgical therapy would also occur.

The cannulation of the hepatic artery at the time of resection has been quite safe. We actually cannulate the gastroduodenal artery to avoid trauma to the hepatic artery. I can recall no thrombosis after resection. Arteriograms are done rather frequently through this catheter, and I think we would have detected thrombosis if it had occurred. Thrombosis of the hepatic artery following ligation is not infrequent however.

In selecting patients for resection of colon metastases in the liver, we have found the interval between treatment of the primary and the metastases really doesn't seem to affect the result or ability to resect.

The individual is a candidate for hepatic lobectomy if there is no disease outside the liver and if the liver lesion can be removed. There will be an occasional patient who may have a solitary metastasis in a lymph node, lung or opposite lobe of the liver that we will resect.

Catecholamines:

Mediator of the Hypermetabolic Response to Thermal Injury

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Hypermetabolism characterizes the metabolic response to thermal injury and the extent of energy production is positively related to the rate of urinary catecholamine excretion. Alpha and beta adrenergic blockade decreased metabolism from 69.6 ± 5.3 Kcal/m^2/hr to 57.4 ± 5.2 ($p < 0.01$), and infusion of 6 μgm epinephrine/minute in normal man significantly increased metabolic rate. Twenty noninfected burned adults with a mean burn size of 45% total body surface (range 7–84%) and four normal controls were studied in an environmental chamber at two or more temperatures between 19 and 33 C with vapor pressure constant at 11.88 mm Hg. All burn patients were hypermetabolic at all temperatures studied and their core and mean skin temperatures were significantly elevated above control values. Between 25 and 33 C ambient, metabolism was unchanged in controls and burns of less than 40% total body surface (48.9 ± 4.6 Kcal/m^2/hr vs. 48.9 ± 4.5), but metabolic rate decreased in larger burns in the warmer environment (72.0 ± 1.9 vs. 65.8 ± 1.7, $p < 0.001$). At 21 C, metabolism and catecholamines increased, except in four nonsurvivors who became hypothermic with decreased catechol elaboration. Metabolic rate in ten patients with bacteremia was below predicted levels while catecholamines were markedly elevated suggesting interference with tissue uptake of the neurohormonal transmitters. Feeding burn patients or administering glucose and insulin improved nitrogen retention and altered substrate flow but did not significantly reduce urinary catecholamines or metabolic rate. Burned patients are internally warm, not externally cold, and catecholamines appear to mediate their increased heat production. Hypermetabolism may be modified by ambient temperature, infection, and pharmacologic means. Alterations in hypothalamic function due to injury, resulting in increased catecholamine elaboration, would explain the metabolic response to thermal injury.

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HYPERMETABOLISM characterizes the metabolic response to thermal injury, and the magnitude of this post-traumatic physiologic alteration is closely related to the extent of injury. Negative nitrogen balance, loss of other intracellular constituents, and a rapid decrease in body weight are consequences of the increase in metabolic activity, and extensive loss of protoplasmic mass may result in severe erosion of energy and protein stores essential to optimal body function. Similarities between the thermally injured and individuals with thyrotoxicosis prompted early metabolic and endocrine studies, but the increased oxygen consumption has not been related to abnormal thyroid function.[10] Increased evaporative water loss from the burn wound results in surface cooling, which could stimulate metabolic activity to maintain normal heat balance and core temperature. The purpose of this study was to define the relationship between surface cooling and hypermetabolism in a controlled ambient environment, to determine the mediator of the profound hypercatabolic response, and to assess the effect of nutritional support on the hypermetabolic response following thermal injury.

Materials and Methods

Patients

Twenty noninfected burn patients, between the ages of 14 and 49 years, were initially studied along with four normal individuals of approximately the same age. Burn patients were selected to represent a range in size of total body surface injury, all except one were

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

male, and none had significant pre-existing disease before thermal injury (Table 1). The patients were studied between the sixth and 33rd postburn days, with the mean day of study being the 11th day following injury. All patients in this initial group were stable following initial resuscitation and during the study period, and were alert and cooperative during the studies. These patients did not have systemic infection, as determined by stable body temperature, absence of clinical signs of infection, and negative blood cultures and endotoxin levels before, during, and after the study period.

The control individuals were healthy male subjects working on the Burn Unit, who were accustomed to the techniques and methodology of respiratory and metabolic testing. There was no history of chronic disease in this group, and all were vigorous, active individuals.

Place of Study

The studies took place in an environmental chamber on the Burn Ward. This rectangular room, previously described in detail,[51] can maintain a selected temperature and humidity between +15 C and +40 C (range ± 2%), limited by a −1.1 C and 35 C dewpoint. The maximum air velocity in the chamber is less than 50 feet per minute at the level of the bed, three feet above the floor. The room maintains good thermal stability with electronic equipment and three individuals present, and clinical monitoring, patient care, and burn wound treatment were continued while each patient was housed in the chamber.

Study Design

The four normals and the first nine patients were studied in the chamber for two consecutive 24-hour periods after entering the chamber at approximately 9:00 A.M. During one 24-hour interval, the environmental temperature was set at 25 C, vapor pressure at 11.88 mm Hg, and, during the other 24-hour study period, the environmental temperature was set at 33 C with the same vapor pressure. The order of the study periods was sequentially altered, and tests were made between the 18th and 24th hours of each study day.

TABLE 1. *Characteristics of Patients Studied at Two or More Ambient Temperatures*

Subjects	Age (Year)	Weight (Kg)	Body Surface Area (m²)	Total Body Burn (Per Cent)	Per Cent Third Degree	Postburn Day Studied	Comment
Control							
1*	25	75.0	1.90	0	0		
2*	20	72.2	1.98	0	0		
3*	23	88.0	2.17	0	0		
4*	34	78.0	2.04	0	0		
Mean	26	78.3	2.02				
Range	20–34	72–88	1.90–2.17				
Patients							
1*	43	69.5	1.82	7	7	8–9	
2	14	59.0	1.72	10	0	7	
3*	28	63.0	1.79	15	2	7–8	
4	17	55.7	1.93	23	4	7	
5*	15	48.0	1.56	26	18	17–18	Associated head injury, tracheostomy.
6*	49	87.5	2.01	34.5	0	8–9	
7	18	70.0	1.79	39	12	8	
8*	24	87.0	2.09	40	14	8–9	
9	43	118.0	2.36	41	3	10	
10	32	50.0	1.48	46	17.5	6	Tracheostomy, female.
11	40	80.0	1.99	50	0	12	
12	38	113.0	2.15	51	22	7	
13*	26	65.9	1.78	52	8	10–11	
14	18	60.5	1.77	53	9.5	14	
15*	34	85.0	2.00	60	16.5	14–15	
16*	18	66.0	1.88	63.5	21.5	10–11	
17	19	96.0	2.23	66	25.5	14	
18	34	77.0	1.91	66.5	39.5	14	Tracheostomy
19	22	48.0	1.59	76	33.5	32–33	Tracheostomy
20*	25	68.0	1.85	84	76	8–9	Tracheostomy
Mean	28	73.4	1.88	45	16.5	11	
Range	14–49	48–118	1.48–2.36	7–84	0–76	6–33	

* Studied over two consecutive 24-hour periods.

As more patients were evaluated, shorter equilibration times were allowed, so that the final 11 patients were studied at two or more temperatures on the same day. These patients entered the chamber in the morning between 6 and 8 A.M., were allowed to rest 4–6 hours in the 33 C environment, and then studied. A new ambient temperature was then selected, a period of equilibration allowed, and additional measurements made. The ambient temperatures selected for this study were 33, 29, 25, 21, and 19 C, and all individuals were studied while in two or more ambient conditions. Vapor pressure was maintained at 11.88 mm Hg throughout the range of ambient temperatures. Patients who were studied in the cooler environments (less than 25 C) were evaluated in these ambient conditions as the final test in the series, and were exposed for only one to two hours to the cooler ambient conditions before the measurements were made. In all other instances, the equilibration period was four hours or more.

Study Methods

The methods of study have been previously described in detail.[51] In summary, all patients were treated by the open method with topical mafenide (Sulfamylon®) cream applied to the burn wounds. The individuals were maintained in the supine position, on a water-resistant mattress, several hours before each test. All patients were fasted three or more hours before and while measurements were made, but received water by the oral or parenteral routes if required to maintain a normal state of hydration. Expiratory gas was collected in two 200 L Douglas bags to determine oxygen consumption and carbon dioxide production. A mouth piece and nose clip or nose plugs were used as an interface with the patient except in those individuals with tracheostomies in whom a direct connection with the tracheostomy tube could be made. All patients were previously trained with the equipment, and application of topical anesthesia to the lips and nose was utilized in patients with facial burns to allow patient acceptance of the equipment by minimizing pain and discomfort. After a steady state was achieved, the expiratory gas was collected and analyzed and the metabolic rate calculated from the oxygen consumption corrected for the respiratory quotient and expressed in Kcal/m² body surface area/hour. Core temperature was continuously monitored from rectal and tympanic probes, and a small hand-held thermocouple was used to measure skin temperature. Between 20 and 50 skin temperatures were taken from areas not in contact with the mattress and the mean skin temperature calculated. These three basic measurements (metabolic rate, core temperature, and mean skin temperature) were carried out at each ambient condition after the period of equilibration.

The core to skin heat transfer coefficient was calculated by the following equation:

$$\text{Core-skin (Kcal/m}^2\text{/hr/C)} = \frac{\text{metabolic rate (Kcal/m}^2\text{/hr)}}{\text{core temp (C)} - \text{skin temp (C)}}$$

In selected patients, urine and/or plasma was collected for the determination of catecholamines, measured by an automated fluorimetric method.[*][46] The urine was collected during the final hour of each ambient study condition, usually by an indwelling catheter which was present in most of these patients, the volume excreted per unit time recorded, the specimen acidified and frozen for analysis. Blood samples were immediately chilled and plasma immediately analyzed for catecholamine levels.

Adrenergic Blockade

Nine studies were performed in six patients (Table 2). The patients were placed in a warm environment in the early morning and allowed to rest and equilibrate with the ambient condition for several hours. Basal studies of pulse rate, blood pressure, respiratory rate, minute ventilation, metabolic rate, serum free fatty acids,

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[*] Total catecholamines will be referred to throughout this paper, but the samples have been fractionated and norepinephrine represents the major (85–95%) catechol component.

TABLE 2. *Description of Patients Studied Following Alpha and Beta Adrenergic Blockade*

Patient	Age (Year)	Weight (Kg)	Body Surface Area (m²)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Postburn Day Studied
1	38	113.0	2.15	51	22	22, 24
2	34	77.0	1.91	66.5	39.5	13
3	18	70.0	1.92	55	18	24, 28, 34
4	22	48.0	1.59	76	33.5	37
5	21	77.7	2.05	28.5	4	9
6	14	52.9	1.54	57	27	27
Mean	24	73.1	1.86	55.5	24.0	24
Range	14–38	48.0–113.0	1.54–2.15	28.5–76	4–39.5	9–37

TABLE 3. *Characteristics of Patients With Bacteremia*

Subject	Age (Years)	Weight (Kg)	Body Surface Area (m²)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Postburn Day Studied	Organism Cultured From Blood	Endotoxin
1	18	70.0	1.92	55	12	8	Staphylococcus aureus	*
2	38	70.5	1.88	56.5	56.5	10	Klebsiella	Positive
3	48	105.0	2.15	61	13	12	Staphylococcus aureus	*
4	39	78.0	2.00	73	49	4	Aeromonas liquefaciens	*
5	34	65.0	1.85	76	28	7	Providencia stuarti	*
6	22	84.0	2.02	82	49	5	E. coli	Positive
7	43	57.4	1.73	45	15	17	Klebsiella	*
8	63	73.6	1.87	31.5	25	17	Providencia stuarti	Negative
9	37	71.6	1.81	67	46	3	Bacillus species	*
10	64	95.2	2.20	49	44	10	Providencia stuarti	*
Mean	41	77.0	1.94	59.5	34	9		
Range	18–64	57.4–105	1.73–2.20	31.5–82.0	12–56.5	3–17		

* Not measured.

blood sugar, and insulin were performed. Blockade was effected by the intravenous administration of phentolamine (Regitine®), 75 mg (alpha blockade) or phentolamine, 75 mg and propanolol (Inderal®), 75 mg infused over 15 to 30 minutes (combined alpha and beta blockade). The adequacy of beta blockade was determined by the absence of response in heart rate or increase in serum free fatty acids following intravenous administration of 2 μgm isoproterenol (Isuprel®). Orthostatic hypotension and nasal stuffiness were present in patients following alpha blockade. After adequate blockade, the initial studies were repeated.

Septic Patients

Eighteen studies were performed in 10 septic individuals (Table 3), all with proven bacteremia demonstrated by a positive blood culture obtained at the time of study. All patients maintained an adequate urine output at the time of study and did not demonstrate hypotension or signs of cardiovascular instability. Metabolic rate, core and skin temperature, urine, and/or plasma catecholamines were measured in selected patients as previously described.

TABLE 4. *Characteristics of Normal Subjects Receiving Epinephrine Infusion*

Subject	Age (Years)	Weight (Kg)	Body Surface Area (m²)	Comment
1	35	76.2	2.02	1a. Four days fasting 1b. Five days fasting (second fast) 1c. Fed
2	39	83.0	2.07	Five days fasting
3	22	72.0	1.95	3a. Four days fasting 3b. Ten days fasting (same fast)
4	18	76.3	1.96	Fed
5	41	107.2	2.19	Fed
6	32	74.9	1.94	Fed
7	26	69.0	1.87	Fed
Mean	30	79.8	2.00	
Range	18–41	69.0–107.2	1.87–2.19	

Epinephrine Infusion

Ten studies were performed in seven normal males who received intravenous epinephrine to evaluate the metabolic and respiratory response to catecholamine infusion. Five of the studies were performed following a 10-hour overnight fast and the remaining five studies were carried out in normals who were fasted and exercised for four to 10 days prior to study (Table 4). The infusion was performed in the environmental chamber which was maintained at 28 C, vapor pressure 11.88 mm Hg, and the subjects entered the study room in the late evening or early morning and slept in the supine position for at least four hours before study. At 7:00 A.M., a large forearm vein was cannulated under local anesthesia and an infusion of .04 M saline started and maintained at a constant rate by infusion pump. After one hour, expiratory gas was collected in Douglas bags as previously described and blood was drawn from the indwelling venous catheter for determination of glucose, blood urea nitrogen, creatinine, free fatty acids, glucagon, cortisol, human growth hormone, and plasma catecholamines. The urine formed during a carefully-timed two to three hour basal period was collected, the volume measured and the specimen processed for determination of urea, creatinine, and catecholamines. After baseline vital signs and electrocardiograms were obtained, the epinephrine infusion was started. The solution, composed as described by Porte,[39] was initially infused slowly, then gradually increased over 10 minutes to volumes comparable to the control and recovery periods, while maintaining an infused dose of 6 μgm epinephrine/minute. Expiratory gas was collected 20–30 and 50–60 minutes after the start of the infusion, and blood and urine samples were obtained after 60 minutes of infusion. The Douglas bag measurements and blood and urine studies were repeated during recovery, one hour post-infusion, and for several consecutive hours in selected subjects.

Nutritional Support, Nitrogen Excretion, and Energy Expenditure Interaction

The effect of nutritional support on metabolic rate and nitrogen loss was evaluated in 43 studies in normal and injured men. The patients, with a mean burn size of 53 per cent of the body surface (Table 5), received a wide range of nutritional support administered by the enteral, parenteral, or enteral-parenteral routes. The normal individuals were studied the day before epinephrine infusion as previously described. Resting metabolic rate was determined in all subjects between 6:00 A.M. and 8:00 A.M. following at least three hours of restriction of *ad libitum* oral caloric intake. However, calories and nitrogen administered by the intravenous route were continued at a constant infusion rate during the measurement period. Blood was obtained for determination of glucose, urea, free fatty acids, insulin, human growth hormone, glucagon, cortisol, and catecholamines and a timed urine specimen was obtained for catecholamine determination. The caloric and nitrogen intake for the accompanying 24-hour period was determined from the composition as listed by the manufacturer, and food intake was determined by the dietitian from known lots of food prepared in the research

TABLE 5. *Characteristics of Subjects Studied*

Subject	Age (Years)	Weight (Kg)	Body Surface Area (m²)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Mean Postburn Day Studied
Control						
1	23	55.8	1.66	0	0	—
Patient						
1	18	52	1.61	58	28.5	a. 25 b. 63
2	17	60.6	1.76	58	14.5	6
3	33	72.6	1.98	50.5	2.5	a. 12 b. 26
4	29	70.3	1.83	47.5	14	15
5	63	73.6	1.87	31.5	25	17
6	64	95.2	2.20	59	54	10
7	51	95.0	2.19	58	27.5	6
8	64	57.2	1.66	39	23	5
9	39	90.0	2.08	23*	10	9
10	29	50.0	1.59	47	0	18
11	60	67.3	1.84	62	53	42
12	25	54.3	1.64	78.5	11	31
13	41	53.0	1.65	60	8	a. 77 b. 85
14	19	77.0	1.98	33.5†	33.5	a. 255 b. 248
15	28	58.0	1.90	75.5	57	a. 49 b. 42
16	16	62.0	1.79	38	14	a. 24 b. 17
17	18	66.0	1.88	64	22	a. 17 b. 24
18	18	66.0	1.88	64	22	a. 32 b. 26
19	21	76.5	1.95	45	26	a. 20 b. 24
20	34	85.0	2.00	60	16.5	a. 24 b. 17
21	22	48.0	1.59	56.5	33.5	a. 44 b. 37
22	14	42.0	1.54	57	27	a. 36 b. 43
Mean	33	66.9	1.84	53	24	29‡
Range	14–64	42.0–95.2	1.54–2.20	23–78.5	0–57	6–255

* Multiple fracture.

† Initial injury 75 per cent; wound partially grafted before transfer.

‡ Excluding patient No. 14.

metabolic kitchen. Urine was collected in 24 hour pools and concentrations of sodium, potassium, creatinine, urea, and total nitrogen determined. Generous estimates of stool losses (2–3 g nitrogen/day) were made for the few patients receiving enteral residue-containing diets. Wound loss was not measured. Insulin was administered as required to those patients with elevated blood or urine glucose and human growth hormone, 10 international units, was given daily by intramuscular injection to nine subjects to evaluate the effect of endogenous reset of insulin output.[52] The mean values of all measurements obtained over three to seven days in the patients were computer-processed with the control data to determine the interaction and effect of caloric and nitrogen support and metabolic rate on nitrogen excretion.

Results

Body Temperature and Heat Transfer

Core temperature did not change significantly between the ambient conditions at 25 and 33 C, but skin

TABLE 6. *Metabolic Rate, Body and Skin Temperatures, and Heat Transfer Coefficient at Different Temperatures*

Subject	Metabolic Rate (Kcal/m^2/hr)	Core Temperature (°C)	Skin Temperature (°C)	Core-Skin Heat Transfer Coefficient (Kcal/m^2/hr/°C)
Measurements at 33C				
Control				
1	39.8	36.7	33.6	12.8
2	34.5	36.9	34.8	16.4
3	37.9	36.9	34.5	15.8
4	33.0	36.9	33.8	10.6
Patients				
1	37.7	38.7	35.6	12.2
2	42.2			
3	43.6	37.5	35.1	14.4
4	60.0			
5	69.4	39.0	37.0	34.7
6	71.0	40.1	37.3	25.4
7	68.8	38.1	36.7	49.1
8	64.9	38.5	36.5	32.4
9	69.4	37.8	36.0	38.5
10	57.5	37.5	36.3	47.9
11	55.0	38.3	36.0	29.3
12	71.7	38.2	34.4	18.8
13	55.6	37.4	35.8	34.7
14	68.0	37.0	34.7	29.6
15	74.8	39.7	36.8	25.8
16	63.6	38.7	36.1	24.2
17	65.8	37.4	35.5	34.6
18	65.2	37.2	35.1	31.0
19a	67.0	38.6		
19b	71.7			
20	71.6	36.9	35.0	37.7
Measurements at 29 C				
Patients				
12	76.8			
16	75.8			
18	70.2	37.6	34.6	23.4
19a	68.3	38.7		
19b	66.3			
Measurements at 25 C				
Control				
1	37.8	36.7	31.4	7.13
2	31.8	36.7	31.3	5.89
3	40.1	37.3	32.0	7.57
4	32.7	36.5	31.0	5.95
Patients				
1	36.9	38.5	31.5	5.27
2	43.0			
3	49.1	38.4	32.5	8.32
4	65.1			
5	62.0	39.5	33.9	11.1
6	72.3	38.8	33.8	14.5
7	67.5	39.7	34.6	13.2
8	58.2	38.5	33.3	11.2
9	69.2	39.0	33.7	13.0
10	70.1	38.5	33.5	14.0
11	62.8	38.4	33.1	11.8
12	78.8	37.5	31.4	12.9
13	61.8	38.5	32.8	10.8
14	76.8	37.9	32.0	13.0

TABLE 6. (*Continued*)

Subject	Metabolic Rate (Kcal/m^2/hr)	Core Temperature (°C)	Skin Temperature (°C)	Core-Skin Heat Transfer Coefficient (Kcal/m^2/hr/°C)
Measurements at 25 C				
Patients				
15	80.0	38.3	34.8	22.9
16	69.9	37.5	33.0	15.5
17	71.6	37.4	33.8	19.9
18	71.4	37.1	32.5	15.5
19a	79.3	38.8		
19b	78.2			
20	79.8	38.2	32.0	12.9
Measurements at 21 C				
Control				
1	41.7	36.7	30.2	6.4
3	40.3	37.0		
4	41.6	36.5	29.8	6.2
Patients				
4	75.8			
5	90.3	38.0	32.2	15.6
7	74.7	39.2	32.2	10.7
9	74.1	39.3	32.3	10.6
10	79.2	38.8	32.2	12.0
14	89.1	37.1	31.4	15.6
15	94.2	37.1		
16	91.9	37.3		
19a	84.0	38.1		
Measurements at 19 C				
Control				
1	48.9	37.0	28.8	6.0
3	49.8	37.0		
4	46.2	36.5		
Patients				
5	89.2			
10	82.7	38.7	32.1	12.5

temperature was altered and moved in the direction of the environmental temperature. However, a marked difference was noted in the core and skin temperatures when comparing normal individuals with burn patients; the average core and skin temperatures were consistently 1–2 C higher in the injured patients when compared with controls (Table 6, 7). This difference was present at all ambient conditions studied between 33 and 25 C, and was also found at the cooler temperature in those patients who were able to increase their metabolic rates in the 21 and 19 C environments. Heat transfer coefficients demonstrated a two-fold increase in core to skin conductance of heat in the burn patients when compared with control individuals, and this two-fold increase was present at all temperatures studied.

Effect of Burn Size and Ambient Temperature on Metabolic Rate

Metabolic rate increased with burn size. The relationship appeared curvilinear, metabolism approaching 70–75 Kcal/m^2/hr when measured in the 33 and 25 C environment as burn size exceeded 50% total body surface (Table 8). In the controls and patients with smaller burns (less than 40% total body surface), there was no change in mean metabolic rate between 33–25 C (48.9 ± 4.6 Kcal/m^2/hr at 33° vs. 48.9 ± 4.5, mean ± S.E.M.). However, it appeared that a consistent decrease in caloric expenditure occurred in patients with larger burn injuries in the warmer environment when compared with 25 C. Mean metabolic rate at 25 C was 72.0 ± 1.9 Kcal/m^2/hr, which decreased to 65.8 ± 1.7 Kcal/m^2/hr at 33 C ($p < 0.001$ by paired t test). As the ambient temperature decreased below 25 C, metabolism increased in both the controls and those patients who eventually survived. However, oxygen consumption rarely exceeded two and one-half times basal levels (Fig. 1). In contrast, four patients with more extensive burns became hypothermic at 21 C, with decreased metabolic rate and a marked fall in core and skin temperature.

TABLE 7. *Measurements From Four Normals and 20 Patients at Two Ambient Temperatures*
(Mean ± S.E.)

	Normal	Burns	p
25 C			
Metabolic rate (Kcal/m^2/hr)	35.6 ± 2.0	66.8 ± 2.6	<0.001
Core temperature (°C)	36.7 ± 0.2	38.4 ± 0.2	<0.001
Skin temperature (°C)	31.4 ± 0.2	33.1 ± 0.2	<0.001
Core skin heat transfer coefficient (Kcal/m^2/hr/°C)	6.6 ± 0.4	13.3 ± 1.0	<0.001
33 C			
Metabolic rate (Kcal/m^2/hr)	36.3 ± 1.6	62.6 ± 2.3	<0.001
Core temperature (°C)	36.9 ± 0.1	38.1 ± 0.2	<0.001
Skin temperature (°C)	34.2 ± 0.3	35.9 ± 0.2	<0.01
Core-skin heat transfer coefficient (Kcal/m^2/hr/°C)	13.9 ± 1.4	30.6 ± 2.5	<0.001

TABLE 8. *Relationship Between Metabolic and Per Cent Total Body Surface Burn at Varying Temperatures*

Ambient Temperature (°C)	Relationship	r^2
21	$y = 42.70 + 1.539\,x - 0.01290x^2$	0.877
25	$y = 35.50 + 1.050\,x - 0.006698x^2$	0.889
33	$y = 36.15 + 1.001\,x - 0.007694x^2$	0.795
T*	$y = 188.8 + 1.211\,x - 10.38T$ $- 0.009274x^2 + 0.1701\,T^2$	0.849

y = Metabolic rate in Kcal/m^2/hr
x = Per cent body surface burn
T = Ambient temperature °C (T 19–33)
$p < 0.05$ for all equations

* Based on 72 measurements of metabolic rate at five different temperatures; hypothermic patients not included.

Relationship Between Metabolic Rate and Catecholamines

The urinary excretion of catecholamines per unit time was related to metabolic rate measured during the same time period. The relationship appeared linear until metabolic rate approached two times basal levels, then increased excretion in urinary catecholamine was associated with only a slight increase in metabolic rate, with the predicted metabolic response never exceeding two and one-half times basal levels for normal man (Fig. 2). The ability to generate additional heat in a cool environment was variable in patients with burns greater than 40% total body surface (Table 9). In four patients with an average burn size of 57% (range 41–76), there was a marked accentuation of hypermetabolism, and this compensatory increase in heat production maintained core temperature and was accompanied by an increase in excretion of urinary catecholamines. However, four patients with a mean burn size of 65% (range 51–84) studied in a cool ambient temperature failed to maintain heat balance and became hypothermic. These "nonresponders" had a sudden decrease in their catecholamine excretions during exposure to the cooler ambient temperature (Fig. 3).

Effect of Adrenergic Blockade

No consistent change in metabolic rate was seen with alpha blockade alone, and the mean basal metabolic rate was 70.7 ± 7.9 Kcal/m^2/hr before blockade and 68.1 ± 4.6 Kcal/m^2/hr following blockade ($n = 3$). However, there was a significant decrease in metabolic rate associated with combined alpha and beta blockade (Table 10) or beta blockade alone, and this response was associated with a decrease in pulse rate, blood pressure, minute ventilation, and free fatty acids. The

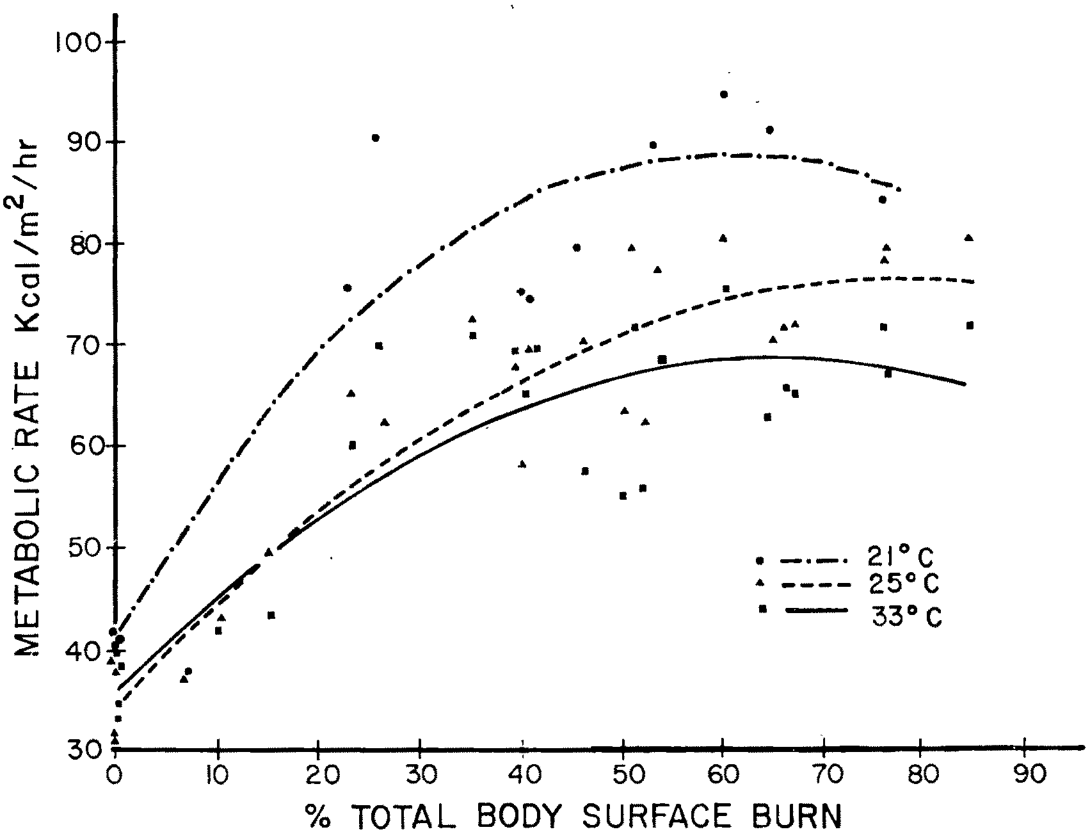

FIG. 1. The relationship between metabolic rate and environmental temperature is demonstrated by the individual regression curves derived for 21, 25, and 33 C ambient (from data listed in Table 6, as calculated from individual equations in Table 8). Both normal men and burn patients increased metabolic rate at 21 C when compared with 25 and 33 C. Only a small decrease in metabolism occurred in patients with large thermal injury studied at 25 and 33 C, and the reduction was in the order of 5–8 Kcal/m²/hr. Metabolic rate did not return to normal when the patients were studied in a warm environment.

dose of propanolol required for competitive blockade of the beta receptor system in these hypermetabolic burn patients was greater than the dose required for normal man, and a persistent sympathetic break-through occurred with the administration of smaller doses of the drug per unit time. Metabolic activity returned to its preblockade level within two to three hours following drug administration.

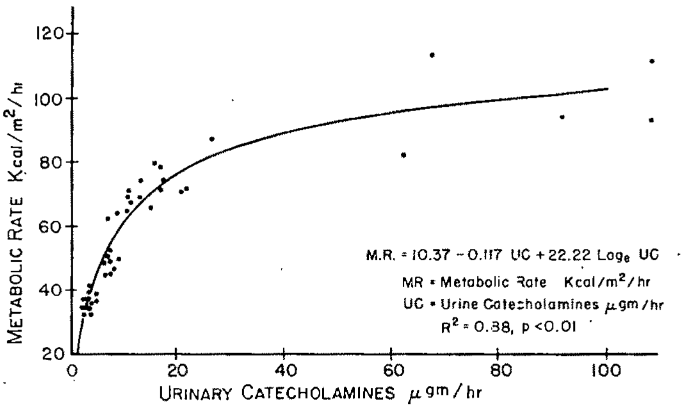

FIG. 2. Relationship between metabolic rate and urinary catecholamines. The response curve to a dose of catecholamine or to nerve stimulation has the shape of a rectangular hyperbole, with a large quantitative difference in response elicited by a small change in dose. As the catecholamines increase, a plateau is reached and increasing doses exert little effect on metabolic rate. Our data expressed as a hyperbolic function is:

$$MR = 100.93 - \frac{580.56}{UC} + \frac{1{,}584.58}{UC^2} - \frac{1351.64}{UC^3}$$

$n = 55$, $r^2 = 0.84$, $p < 0.05$.

Septic Patients

Metabolic rate was significantly decreased in 10 septic patients studied. The mean metabolic rate was 50.3 ± 2.2 Kcal/m²/hr compared with predicted or measured rates during nonseptic intervals which averaged 73.0 ± 1.2 Kcal/m²/hr (Table 11). Urinary catecholamines were markedly elevated in these patients, averaging 910.8 ± 406 μgm/hr, and this level of catecholamine excretion was inappropriately high for the metabolic response measured (Fig. 2).

Epinephrine Infusion

Metabolic rate increased with the infusion of 6 μgm epinephrine/minute in normal man when compared with the basal period (Table 12). The hypermetabolism was accompanied by an increase in respiratory rate and minute ventilation, and these alterations in metabolic and respiratory function returned toward normal following infusion. Blood glucose, free fatty acid, and glucagon increased, growth hormone fell, and insulin and glucocorticoids remained unchanged during catecholamine infusions, alterations consistent with pre-

TABLE 9. *Variable Response of Patients With Large Thermal Injury to Decreasing Environmental Temperature*

	Metaboic Rate (Kcal/m^2/hr)					Urinary Catechols (μgm/hr)					Skin Temperature (C)					Tympanic Temperature (C)				
Patient	33	29	25	21	19	33	29	25	21	19	33	29	25	21	19	33	29	25	21	19
1	69.4		69.2	74.0		13.5		12.0	13.5		36.0		33.7	32.3		37.8		39.0	39.3	
2	57.6		70.0	79.2	82.7	8.4		28.0	91.0		36.3		33.5	32.2	32.1	37.5		38.5	38.8	38.7
3	63.6		69.9	91.9		15.3		18.5	34.2		36.1		33.0			38.7		37.5		
4	67.0	66.3	79.3	84.0		6.6	8.2	16.2	96.0							38.6	38.7	38.8	38.1	
5	63.5	52.6	50.8			9.2	11.8	10.2			34.8	33.6	32.3			37.2	36.8	36.2		
6	71.7		78.7	69.3		22		17.5	10.8		34.4		31.4	29.5		38.2		37.5	37.9	
7	84.0		83.2	57.6							34.6		32.1	30.4		36.3		35.4	35.9	
8	80.2	87.0	81.5			22.5	27.6	12.5			34.5	33.3	31.5			37.3	37.0	36.5		
9	65.2	72.3	71.4	68.4		16.8		17.6	7.6		35.1	34.6	32.5	30.9		37.2	36.9	37.1	36.7	
10	71.4		79.7	67.0							35.0		32.0	29.3		37.0		38.2	38.0	

viously reported observations.[17,27,36,39] Excretion of urea nitrogen was not altered throughout the study in the fed patients (52.6 ± 10.6 mg urea nitrogen/hr pre-infusion, 48.5 ± 9.7 during infusion, and 46.3 ± 12.0 post-infusion), but nitrogen loss increased with infusion in the fasting subjects (44.0 ± 5.8 mg/hr pre-infusion, 60.6 ± 7.2 during infusion, 48.6 ± 6.0 post-infusion, $p < 0.05$ difference between infusion period and pre-infusion and post-infusion period). No significant alteration in blood urea nitrogen occurred during the study.

Nutritional Support, Nitrogen Excretion, and Energy Expenditure Interaction

Increased nitrogen excretion was associated with hypermetabolism and/or with increased dietary protein intake. Nitrogen excretion decreased with administration of nonprotein calories and/or an increase in plasma insulin (Table 13, 14). Metabolic rate was related to urinary catecholamines as previously described, and a positive correlation also existed between glucagon levels and catecholamine excretion. Each of these three variables relates in similar fashion to protein metabolism, with a positive correlation existing between urinary catecholamines, metabolic rate, or glucagon and nitrogen excretion. Metabolic rate and catecholamine excretion were not reduced by calorie and nitrogen administration, confirming previous studies,[53] but the protein-wasting resulting from the hypermetabolism was diminished or reversed with nonprotein calorie intake, nitrogen administration, and/or maneuvers which increased basal insulin levels (Table 14).

TABLE 9A. *Description of Patients Studied: Multiple Temperatures*

Patient	Age	Weight (Kg)	Body Surface Area (m^2)	Total Body Surface Burn (Per Cent)	Per Cent 3°	Postburn Day Studied
1	43	118.0	2.36	41	3	10
2	32	50.0	1.48	46	17.5	6
3	18	66.0	1.88	63.5	21.5	10–11
4	22	48.0	1.59	76	33.5	33
5	74	66.4	1.71	46	27	6
6	38	113.0	2.15	51	22	7
7	22	64.0	1.86	57.5	19.5	7
8	60	67.3	1.84	62	53	11
9	34	77.0	1.91	66.5	39.5	14
10	25	68.0	1.85	84	76	8–9

Discussion

Hypermetabolism characterizes the metabolic response following thermal injury, and this alteration in metabolic activity correlates well with increased evaporative water loss from the burn wound.[28] Decreasing wet or dry heat loss in small animals has been reported to return metabolic rate towards normal.[6,37] Burn patients treated in a warm environment (32 C) demonstrate lower metabolic rates than when treated in a cool environment (22 C),[1] and this evidence has been interpreted to support the thesis that hypermetabolism in the burn patient is a response to increased surface cooling due to increased evaporative water loss. In contrast, however, Zawacki and associates covered burn wounds with a water-impermeable membrane and thus blocked evaporative water loss, but found no consistent alterations in metabolic rate in burn patients at approximately 25 C ambient temperature.[56]

In this study, the average core temperature of the burn patients was elevated above normal, and the mean skin temperature was increased in all nonhypothermic patients at all ambient conditions studied when compared with normal man, demonstrating that the burn patients are internally warm and not externally cold. The usual response of normal man to a cold environment involves both vasoconstriction to achieve core insulation and decreased sweat secretion. Further cooling results in hypermetabolism, which occurs in an individual with a normal or slightly decreased core temperature and a cool dry skin. Our patients, however, were hypermetabolic in a warm environment, with elevated core and skin temperatures, and, when equili-

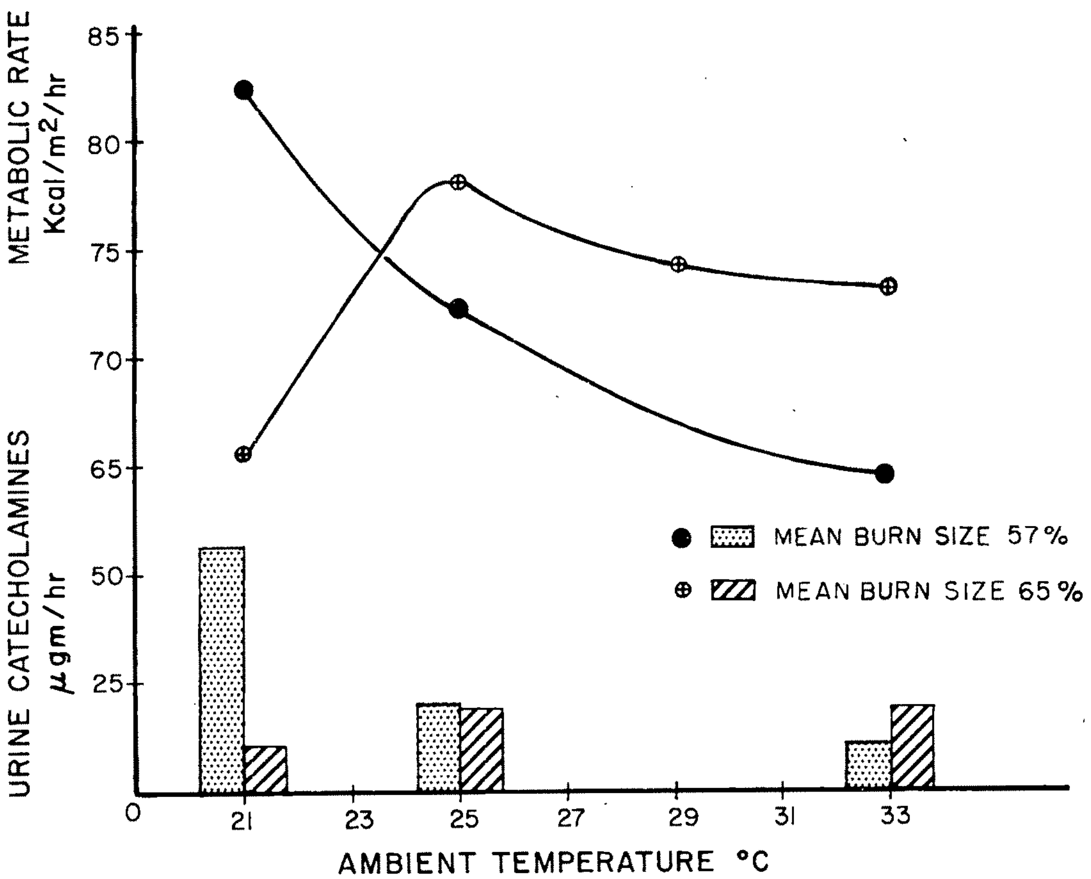

FIG. 3. Failure to respond to cooling in patients with large thermal injury. The ability to generate additional heat to cold stress is variable in patients with large thermal injury, but appears to depend primarily on burn size. Individuals with smaller injuries and available metabolic reserve (mean values from Patients 1–4, Table 9) respond to cooling by increasing metabolic rate and this response is associated with increased urinary catecholamines (solid dots, stippled bars), while others (Patients 6, 7, 9, 10) lack catechol or tissue reserves, fail to maintain heat balance, and become hypothermic (crossed dots). These "nonresponders" are apparently at maximal rates of energy production and cannot respond appropriately to catechol mediated stress, such as cooling, infection, and hemorrhage. Two elderly patients studied (No. 5 and 8) reacted physiologically like poikilotherms in the varying ambient temperatures.

brated with a cooler environment, continued or slightly increased their hypermetabolism while their core and skin temperature remained higher than those of the normal controls. Evaporative water loss and surface cooling in the burn patient is not the primary stimulus for the hypermetabolic state but rather the hypermetabolic response is related to an endogenous reset in metabolic activity. Vaporizational heat loss serves as a convenient route for transfer of this large heat load from the body.

TABLE 10. *Effect of Alpha and Beta Blockade on Hypermetabolism Following Thermal Injury*

	Pulse (Beats/Min)		Blood Pressure (mmHg)		Respiratory Rate (Breaths/Min)		Minute Ventilation (L/Min)		Metabolic Rate (Kcal/m²/Hr)		Free Fatty Acids (mEq/L)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Alpha Blockade												
1a	120	110			29.0	32.9	38.2	29.1	80.2	76.8	2.0	8.0
1b	126	118			25.6	24.9	24.3	19.7	76.8	66.7	1.3	3.5
3	100	84	142/70	120/50	12.0	12.5	12.1	16.1	55.0	60.9		
Mean*	115	104			22.2	23.4	24.9	21.6	70.7	68.1	1.6	5.8
S.E.	8	10			5.2	5.9	7.5	3.9	7.9	4.6	0.4	2.2
Alpha and Beta Blockade												
2	118	84	116/72	88/52	40.0	38.0	35.4	32.2	68.0	59.9	4.0	1.7
3a	96	88	160/82	124/68	16.0	19.5	18.0	9.4	66.8	44.9	4.6	2.3
3b	98	84	128/80	100/70	22.7	24.0	12.0	10.1	46.9	42.4	5.0	3.5
4	120	96	120/100	90/—	17.7	14.0	22.6	19.0	78.7	64.7		
5	120	84	118/80	80/60	19.4	17.5	19.4	17.5	72.0	55.8	4.9	3.6
6	144	96	115/80	86/—	17.7	14.6	20.5	17.2	85.1	76.6	2.2	1.3
Mean	116	89	126/82	95/63	22.2	21.3	21.3	17.6	69.6	57.4	4.1	2.5
S.E.	7	2	7/4	6/4	3.7	3.7	3.2	3.4	5.3	5.2	0.5	0.5
p	<0.01		<0.001/<0.01		>0.10		<0.02		<0.01		<0.01	

* Effect not different by paired t test.

TABLE 11. *Metabolic Requirements in Patients With Bacteremia*

Patient	Ambient Temperature	Metabolic Rate (Kcal/m²/Hr)		Urinary Catecholamines (μgm/Hr)
		Predicted*	Measured	
1	21	84.5	66.2	668
	25	74.3	51.7	195
	33	70.2	58.8	22.8
2	25	74.5	40.6	
	29	69.8	35.6	
3	33	71.0	60.4	
4	25	74.7	54.5	
5	21	84.4	51.3	
	25	74.2	53.8	
	29	69.4	48.2	
	33	70.1	45.5	
6	25	72.7	35.9	
	29	67.9	35.9	
7	25	71.4	44.4	930
	25	71.4	54.0	1,391
8	25	64.7	54.7	264
9	25	75.2	52.0	3,498
10	25	72.8	62.3	318

* Based on regression equation (Table 8), measurements in five patients before septic episode are comparable to the predicted values.

The inability of the burn patient to return metabolic rate to normal levels in a warm environment is comparable to reports by Swedish investigators, who found a decrease of metabolic rate between 22 and 32 C, but failed to demonstrate a return of metabolism to basal levels in patients in warm dry air.[1] As noted in the present study, hypermetabolism occurs in normal man at 21 C, and other reports suggest that the critical temperature for man is approximately 24–25 C (range 22–27).[12,50] Exposure to ambient conditions below this temperature results in hypermetabolism. Increased heat production, accentuated nitrogen excretion, and weight loss occur in fasted normal man,[33] burn patients,[4] and individuals with fractures[11] when studied below critical temperature, and this is a normal physiologic response to cold exposure. We interpret our data and the other clinical reports as indicating that warm environments do not abate the metabolic response to injury but rather that cold environments accentuate or augment the post-traumatic metabolic response to injury.

What is the mediator for the increased energy production following thermal injury? Hormonal stimulation of heat production occurs with the elaboration of thyroid hormones or catecholamines.[31] Thyroid function has been carefully studied and hyperthyroidism does not appear to cause the increased oxygen consumption following burn trauma.[10] Catecholamines are elevated following thermal injury,[18] and adrenergic activity, as measured by urinary excretion of catecholamines,[47] is related to the extent of stress or severity of injury and to the oxygen consumption of the patient.[29] With wound healing, catecholamines and metabolic rate return to normal.

Cannon demonstrated the importance of the sympathetic nervous system to the maintenance of body homeostasis following a wide variety of stresses, and suggested that increased heat production, which characteristically occurs with sympathoadrenal discharge, may be one of the most important physiologic effects of these hormones.[7] Catecholamines infused into animals increase metabolic rate, and epinephrine or norepinephrine[42] infusions in normal man produce hypermetabolism. Rats in which adrenergic function is completely blocked die in three hours when exposed to 4 C ambient environment, while normal animals

TABLE 12*A*. *Measurements Before, During, and After Epinephrine Infusion in Normal Man*

	Basal					Infusion*				
Subject	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/(Hr)
Fasting										
1a	5.22	4.8	1.08	0.68	32.0	7.53	6.2	1.25	0.66	45.8
1b	6.05	4.3	1.42	0.67	34.8	9.32	14.2	0.66	0.64	45.3
2	6.06	8.6	0.71	0.70	34.3	9.33	9.9	0.94	0.68	52.0
3a	6.28	11.9	0.52	0.70	38.3	8.06	11.7	0.69	0.69	48.4
3b	4.68	9.5	0.49	0.70	31.5	7.08	11.9	0.59	0.58	42.6
Fed										
1c	4.88	4.8	1.04	0.72	31.9	7.01	5.0	1.45	0.70	44.3
4	4.29	4.3	1.00	0.68	33.3	7.90	9.1	0.90	0.76	49.0
5	8.70	12.8	0.68	0.68	36.3	11.31	15.4	0.74	0.69	48.5
6	5.26	5.9	0.89	0.71	34.3	7.44	8.4	0.89	0.67	44.0
7	5.33	8.2	0.64	0.78	31.4	6.42	6.6	0.97	0.77	41.7
Mean	5.68	7.51	0.85	0.70	33.8	8.14	9.8	0.91	0.68	46.2
S.E.	0.39	1.00	0.09	0.01	0.7	0.46	1.1	0.09	0.02	1.0
						p† <0.001	<0.05	>0.50	>0.10	<0.001

* Mean measurements from four Douglas bag collections.

† Paired t-test compared with basal.

TABLE 12*B*. *Measurements Before, During, and After Epinephrine Infusion in Normal Man*

	One-Hour Postinfusion					Two-Hour Postinfusion				
Subject	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)	Minute Ventilation (L/Min)	Frequency (Resp/Min)	Tidal Volume (L)	Respiratory Quotient	Metabolic Rate (Kcal/m²/Hr)
Fasting										
1a	6.68	4.8	1.38	0.70	41.6					
1b	6.71	4.4	1.52	0.69	37.3	6.35	4.0	1.55	0.70	36.4
2	6.89	6.8	1.01	0.70	41.8					
3a	6.46	11.2	0.58	0.71	39.0	5.07	10.8	0.47	0.70	37.7
3b	6.36	11.0	0.58	0.68	36.1					
Fed										
1c	4.80	3.0	1.59	0.70	34.1	5.44	2.9	1.90	0.70	34.6
4	5.41	8.1	0.67	0.71	35.0					
5	12.62	14.2	0.89	0.77	43.6					
6	5.87	4.7	1.25	0.72	35.6					
7	4.84	7.4	0.66	0.72	32.7					
Mean	6.66	7.6	1.01	0.71	37.7					
S.E.	0.70	1.1	0.13	0.008	1.2					

adjust to the temperature by increasing their metabolic rate.[5] Totally sympathectomized cats can be maintained in a carefully controlled laboratory environment, yet are unable to defend against hypoxia, fluid restriction, stresses of environmental temperature, hemorrhage, and exercise.[8] The importance of the adrenergic beta receptors in mediating calorigenesis was demonstrated by Estler and Ammon,[13] and was confirmed in our patient studies. Alpha blockade did not affect heat production in the burn patients, while combined alpha and beta blockade and beta blockade alone significantly reduced metabolic rate. Thus, the increased heat production appears to be mediated by catecholamines, which have a direct effect on cellular calorigenic activity. However, the increase in sympathetic activity and catecholamine elaboration in the burn patients is not the immediate effect of cold stimulation of peripheral or central nervous system receptors.

Other factors interact with the basic reset in internal metabolic activity to alter the final sympathetic-mediated physiologic response. First, ambient temperature affects the basic reset to increase metabolic rate as environmental temperature falls below 25 C. Moreover, patients with burns greater than 40% of the total body surface demonstrate a slight reduction in heat production between 25 and 33 C. This response is due to the inability of patients with large thermal injury to achieve adequate core to skin insulation and reduce surface temperature in response to cooling,[51] as demonstrated in this study by the increased core-skin heat conduction in the burn patients as compared to controls. One explanation for the impairment in insulative function and inability to regulate skin temperature and limit heat loss is that tissue injury results in increased blood flow to the skin, apparently to aid oxygenation and improve nutrient supply to insure wound healing. This thesis is supported by studies in burns demonstrating a hyperdynamic circulatory state, increased cutaneous blood flow, and peripheral shunting, associated with normal visceral flow and oxygen extraction.[26]

Secondly, the ability to respond to a stimulus requiring catecholamine-mediated calorigenesis depends upon the availability of catecholamine reserves and the ability of tissue to respond to increased catechol stimuli. Goodall and Haynes[19] reported that patients with large thermal injury may show depletion of adrenal medullary catecholamines, and Goodall and Moncrief[20] demonstrated that severe thermal injury could deplete monoamine stores in the sympathetic nerve endings and sympathetic ganglia. Labelled dopamine administered to patients with large thermal injury demonstrated an increased turnover compared with normals, and there was a marked shift of this precursor toward noradrenaline synthesis and utilization.[21] The turnover and excretion of dopamine was so rapid that Goodall suggested precursors be administered to burn patients to insure adequate adrenergic stores. These study patients with burns of more than 40% of the body surface appear to maintain maximal or near maximal rates of catechol synthesis and utilization. Exposing these patients to a cool environment (21 C) results in a mild cold stress, ordinarily a stimulus for the elaboration of additional catecholamines. Patients who eventually survived responded by increasing heat production as a result of increased elaboration of catecholamines. In contrast, the patients who lacked catecholamine reserve or tissue responsiveness to these mediators failed to generate additional heat to maintain heat balance in the 21 C environment and became hypothermic, with the decrease in catecholamine excretion reflecting a predictable hormonal response during hypothermia. All of these nonresponding patients subsequently died from complica-

TABLE 13. *Metabolic Rate, Caloric and Nitrogen Intake, Nitrogen Excretion, and Basal Insulin in Normal and Injured Man*

Subject	Nitrogen Excretion (gm/m²/Day)	Metabolic Rate (Kcal/m²/Day)	Nitrogen Intake (gm/m²/Day)	Non-Protein Caloric Intake (Kcal/m²/Day)	Insulin (μU/ml)
Controls-Fed					
1	7.90	888	9.00	1196	20.7
1c*	8.06	769	9.12	810	17.5
4*	7.52	808	9.00	1014	13.8
5*	8.23	871	10.10	1104	14.0
6*	7.70	889	8.71	1133	9.4
7*	8.52	835	10.50	990	17.0
Controls-Fasting					
1b*	5.33	750	0	0	9.5
2*	4.33	823	0	0	11.0
3b*	8.93	919	0	0	12.5
Patients					
1a	8.79	2030	6.52	2258	6.0
1b	11.42	1545	20.20	2468	24
2	11.52	1718	5.68	1392	9.5
3a	14.0	2244	12.38	1436	17.5
3b	10.1	1404	13.00	1893	13.0
4	13.10	1524	15.84	1654	14.5
5	10.40	1312	9.51	1187	24
6	7.92	1495	0	913	37
7	12.44	1680	0	548	19.5
8	7.99	1022	4.34	850	13.5
9	15.74	1608	0	515	36
10	10.48	2200	8.01	2460	40
11	9.9	1526	8.50	1280	61
12	7.5	2026	7.75	2006	25
13a	8.6	1375	12.2	2009	17
13b	4.4	1375	12.2	2009	31
14a	6.0	1207	15.8	2055	23
14b	4.7	1207	15.8	2055	80
15a	9.7	1716	13.6	1934	24
15b	6.5	1716	13.6	1934	49
16a	12.8	1658	17.1	1907	17.5
16b	9.9	1658	17.1	1907	23.7
17a	15.1	1616	16.1	1466	10.7
17b	10.7	1666	16.1	1466	20.1
18a	9.1	906	13.5	1458	26
18b	7.3	906	13.5	1458	42
19a	15.6	1440	17.5	1733	9.2
19b	12.5	1440	17.5	1733	28
20a	15.0	1894	13.8	1560	12.0
20b	16.0	1894	13.8	1560	15.5
21a	12.7	1878	22.0	2450	30
21b	9.5	1878	22.0	2450	46
22a	12.6	1794	14.0	1841	16.8
22b	8.0	1794	14.0	1841	45.6

* Subjects described in Table 4.

tions of their injury. Like Cannon's sympathectomized cats, the nonresponders lacked homeostatic reserve, for injury had reset their rate of energy production at a maximum level. Additional sympathetic nervous system reserve was unavailable for catecholamine-mediated responses to cooling, infection, or hemorrhage.

The third factor which interacts with the internal post-traumatic reset in metabolic activity is associated injuries and infection. Burn patients with associated injuries, such as fractures, head injuries, or visceral trauma, have metabolic rates which exceed values predicted for their burn wound size. This, however, only occurs if the burn injury is smaller than 40% of the total body surface and their metabolic activity is not at maximal levels. Associated injuries in patients with large burns exert little or no additional metabolic effect, for the thermal injury has already caused a maximal stress response.

Infection is commonly associated with a febrile response and an increase in metabolic rate.[9] This is true in patients with small burns who have "calorigenic reserve," for infection will cause an additional expenditure of energy which abates as the septic process is controlled. Sepsis evokes a sympathoadrenal response,[14,24,25] but the

TABLE 14. *Mathematical Relationships Between Energy Production, Food Intake, Nitrogen Excretion, and Basal Insulin*

N_{IN} = Nitrogen Intake (gm/m²/Day)
N_{EXC} = Nitrogen Excretion (gm/m²/Day)
N_{BAL} = Nitrogen Balance $[N_{IN} - N_{EXC}]$ (gm/m²/Day)
MR = Metabolic Rate (Kcal/m²/Day)
NPC = Non-Protein Caloric Intake (Kcal/m²/Day)
BI = Basal Insulin (μU/ml)
$p < 0.05$, Factors listed on order of F-Ratio
$N_{EXC} = -1.398 + 0.4153\ N_{IN} - 0.004530\ NPC - 0.07746\ BI + 0.01696\ MR - 0.000004\ MR^2$
$n = 35$ (Eight values with error > 25 per cent were eliminated from Table 13)
$r^2 = 0.8246$
$N_{BAL} = -3.830 + 0.6072\ N_{IN} - 0.006599\ MR + 0.004376\ NPC + 0.05570\ BI$
$n = 43$
$r = 0.9001$
(All data listed in Table 13)

physiologic effects of the catecholamines appear to be blunted as a consequence of the infection in patients with large thermal injury, a response similar to pharmacologic competitive adrenergic blockade. The marked increase in catecholamines in the blood and urine of our septic patients was accompanied by an inappropriately low physiologic response to these neurohumoral mediators, resulting in inadequate heat production, increased skin blood flow, and progressive hypothermia. While these high levels of catecholamines may represent a massive response of the sympathetic nervous system to infection associated with tissue refractoriness, these infected patients are similar to others with large thermal injury with limited catecholamine stores and minimal homeostatic reserve. This large increase in excretion of urinary catecholamines is observed when the tissue inactivation process is inhibited, as seen with receptor blockade, which results in transmitter overflow[34] and a diminution of the end-organ physiologic response. We have not observed in nonseptic burn patients the very high plasma and urine concentrations of catecholamines measured in the infected patients.

Associated with the hypermetabolic response following injury is the negative nitrogen balance and loss of intracellular constituents. Like the post-traumatic hypermetabolism, the magnitude of the negative nitrogen balance is related to the extent of injury.[35] Studies in burn patients suggest that increased sympathetic activiy may result in a hormonal environment which favors proteolysis, gluconeogenesis, and ureagenesis.[54] Catecholamines stimulate glucagon elaboration[17] and suppress insulin release,[39] a hormonal setting which favors hepatic glucose production and ureagenesis.[44] Sympathetic activity returns to normal with closure of the burn wound, and at that time a normal relationship between insulin, catecholamines, and glucagon is re-established, associated with weight stabilization and weight gain.

Those factors which affect protein metabolism in injured man can be identified by inspection or analysis of our data. First, the influence of dietary factors: protein intake increases excretion of urinary nitrogen, and nonprotein calorie intake decreases nitrogen excretion. The nitrogen conserving effect of calorie intake is in part mediated by insulin stimulation, and a variety of metabolic studies confirm the positive correlation between protein sparing and insulin during calorie administration following injury. On the other hand, our data indicate that metabolic rate describes an effect on protein metabolism which is antagonistic to the anabolic activity of insulin. Nitrogen metabolism appears to be determined by the interaction between insulin (the dominant anabolic hormone) and sympathetic activity, as measured or expressed by catecholamine excretion rate, metabolic rate, or glucagon. Thus, a specific relationship between nitrogen balance and nitrogen and nonprotein calorie intake exists in injured man, if an adjustment is made for the various factors which alter insulin levels (such as the proportion of fat and carbohydrate in the nonprotein component of the diet, the route of food administration, and the exogenous administration of insulin) and the level of sympathetic activity in the patient. Finally, protein and calorie intake does not diminish the hypermetabolic response to injury, but feeding the patient minimizes or prevents severe protein wasting which may impair organ function.

Increased sympathetic activity occurs following burn injury but is also characteristic of major trauma,[15] cold exposure,[31] severe exercise,[48] infection,[25] shock,[49] hypoxia,[40] anxiety,[43] and other stresses.[45] The sympathetic nervous system directs the mobilization of substrate from tissue stores to provide specific body fuels by having direct effects on body tissues, by altering circulation, and by interacting with other hormones to regulate substrate flow.[30,41] In addition, catecholamines stimulate calorigenesis by a direct effect on cellular metabolic activity to increase heat production.[23] As the stress decreases, sympathetic activity falls to normal, and, with parasympathetic activity, substrate is directed into tissue synthesis and energy storage. Early physiologists recognized this interaction and characterized the sympathetic nervous activity as catabolic, directing the expenditure of energy, and the parasympathetic activity as anabolic, conserving and restoring body fuel.[2]

What then directs and regulates the sympathetic response following thermal injury? The reflex arc is composed of nervous and/or humoral afferent stimuli to the hypothalamus, which in turn initiate responses along sympathetic and motor efferent pathways.[22,32] Stimulation of the ventral medial nucleus of the hypothalamus in animals produces increased sympathetic activity associated with hyperthermia, hyperglycemia, hyperglucagonemia, and insulinopenia.[16] This and other related hypothalamic nuclei integrate the function of the autonomic nervous system and regulate body temperature, the flow of energy substrates, metabolic rate, and other endocrine functions in a coordinated manner. The metabolic control center of the hypothalamus is closely integrated with the activity of the thermal regulatory centers, specifically with the posterior area described by Isenschmidt and Krehl, which regulates the cold response, and some authors have suggested that this thermal regulatory area and the sympathetic center are the same.[3]

Burn patients appear to have reset their thermal regulatory set-point upward, thus increasing the discharge of sympathetic impulses to stimulate heat production and substrate mobilization in order to maintain a new and elevated core temperature. Burn patients increase metabolic rate in a cool environment at core and skin temperatures above the set points recorded for normal man.[51] If burn patients are allowed to control the ambient temperature, they select "comfort" environments between 28 and 35 C and maintain elevated core and skin temperatures while subjectively comfortable.[55] Fasting blood glucose is above normal levels following injury, and the hyperglycemia is related to the extent of the injury and the increased catecholamine excretion rate. Fasting levels of growth hormone are also elevated above control values in spite of hyperglycemia.[38] Afferent neural or hormonal stimuli from the injury appear to influence hypothalamic centers to elevate central temperature (and possibly metabolic) set point, increasing sympathetic nervous system activity, and resulting in the hypermetabolism characteristic of thermal injury.

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DISCUSSION

DR. TIMOTHY S. HARRISON (Ann Arbor, Michigan): I would like to emphasize two aspects of their data which I consider particularly important.

The first deals with the observation that beta adrenergic receptor blockade eliminates the hypermetabolism of burned patients. This establishes that the hypermetabolic response to the burn injury is, in fact, mediated by the catecholamines, something which has been strongly suggested but not conclusively proved up until this time.

The second point of emphasis is that in burn patients in whom catecholamines are exhausted, there is insufficient precursor, these formerly hypermetabolic patients will, in fact, die. This is a definable source of burn mortality, and one which can be influenced favorably as Goodall and more recently, Dr. Wilmore have shown, by the administration of the appropriate precursor, dopamine or its equivalent.

If I may, I will show one slide briefly, (slide) which is a photomicrograph of the myocardium, and shows here a focal necrosis. This type of lesion can be produced by catecholamines in any species in which it is attempted.

This lesion also, interestingly enough, has been found in pheochromocytoma patients in a recent study from the Mayo Clinic. This particular section represents none of these situations, however, but, in fact, is the myocardium of a hypermetabolic burn patient with prolonged catecholamine hypersecretion. This patient died! These lesions were described, about 20 years ago, by Dr. Carl Moyer before this Association. He felt confident that this was a source of major burn mortality about which very little could be done. We feel the catecholamine hypersecretion was implicated strongly in this patient's death. Therefore, with a hyperreactive adrenergic nervous system one can define another source of burn mortality about which very little has been done therapeutically.

In the past 20 years nothing has altered the mortality from major thermal burns. I think insights such as those provided by the work described this afternoon will enable us to be more effective toward these patients than we have been up until now.

Dr. George H. A. Clowes, Jr. (Boston): Are the catecholamines really the factor that pushes the metabolic rate? Alternatively, are they just one of several that participate? The endocrines that we really have to worry about are insulin, glucagon, the catecholamines and perhaps the tissue injury factor.

We do know that such a thing exists in burns. We can prove that an inappropriate vasodilation takes place in an experimental animal, if one takes a fraction of the plasma from a burn patient or other animal and infuses it into a leg. We can see that vasodilation occurs then.

This is just an example of the kind of huge cardiac output that is required for a burn patient to maintain his equilibrium and to satisfy his metabolic requirements.

(Slide) This is a case studied some time ago, when we were making an attempt to measure catecholamines in the plasma. As you know, that's a very unsatisfactory type of measurement, and we have never emphasized it much, but this one tends to illustrate the point. The patient started with high cardiac output, when his cardiac output decreased, and his catecholamines started to rise in the plasma at that time. Was the elevated plasma catecholamine to enable him to maintain a high cardiac output that would satisfy the high circulatory requirements or was it to maintain a high metabolic rate?

If we look at the matter of insulin, it does rise in the high-output state, but in a shock state, a low cardiac output, it tends to be low, as shown by Hebert and many others, as well as ourselves in the septic shock state.

The glucagon part of the picture, I think, is purely secondary. It's a stimulator of more carbohydrate production in the liver, and plays a major role, but probably does not influence the periphery, where the metabolic control appears to lie, as I pointed out previously.

The difference between those patients who did not respond and the seriously septic patients that had low metabolic rates compared to the others may be related to the action of endotoxin. Recently we have been able to show by animal experiments that the endotoxin model really does not resemble the typical clinical septic state. It poisons the liver, if you like, and glucose production falls off very rapidly. The animal does not deteriorate until the circulating glucose has fallen to low levels. I simply throw this out because the septic patients may have been suffering from some such phenomenon.

It does seem to me that this particular piece of work has proven beyond any question the value of the warm ambient atmosphere, and that the metabolic rates—when you examine the paper, you will see that they are distinctly lower to maintain core temperature at the higher ambient temperatures. Therefore, I think we have to take exception to Dr. Codwell's statement.

The only other point I would make is that whatever the tissue injury factor is, it may play a role in altering the responsiveness of the hypothalamus, where heat regulation takes place. We know that these people tend to be alkylotic—in other words, the respiratory system is overly sensitive to CO_2—and I think that probably herein lies this change of core temperature regulation.

Now, it also may be that these burned people, with their inappropriate vasodilation, are unable to constrict their skin vessels the way a normal individual does, and therefore they require a greater heat production and circulation.

Dr. Douglas W. Wilmore (Closing discussion): As we studied these patients at multiple ambient temperatures—21, 25 and 33 C—we realized that patients decrease their metabolic rate as the room temperature increased.

However, this is a similar response seen in normal man with a decrease in metabolic rate as ambient temperature increased from 21 to 33.

Barr and associates compared 22 with 32 ambient temperature and our data are comparable and show a decrease in metabolic rate when meansured in the 33 C environment. Comparing temperatures of 21 C with 33 C move patients across their critical temperature. Normal man responds at 21 by increasing his metabolic rate, and this is a normal response to cold.

Our studies demonstrate that cool temperature accentuates or accelerates the hypermetabolic response to injury. At no time does the warm ambient temperature return metabolism down to normal levels, and this is comparable with the data from other investigators, showing that the metabolism never returns to normal by caring for these patients in a warm environment.

Burn patients are internally warm, and not cold. Their core temperature is 38–39 C and their skin temperature at 25 ambient is two degrees warmer than normal man. They are not surface cooling in the classic sense, but are internally warm.

Dr. Harrison and Dr. Clowes and Dr. Levenson all pointed out some of the interesting and interrelating factors that have to do with the entire metabolic response in injured man. Thank you very much for your comments. There is no question that the metabolic response is closely related to the circulatory response, and some of the limitations that we see in the ability to generate additional heat may be rate limited by circulation.

Dr. Levenson asked about the change of heat balance and heat transfer and, we have studied these patients and measured radiation conduction, convection and evaporation. By altering room temperature and not changing metabolism or core temperature, we are essentially changing routes of heat transfer from the body.

The temperatures of the burned skin are slightly cooler than the temperatures of the nonburned skin, but still skin temperatures in thermally injured man are a degree or so warmer than what is found in normal man.

How is metabolic rate in traumatized men altered with food intake? Coleman and DuBois fed patients with typhoid fever and noted that the specific dynamic action of food in hypermetabolic infected patients was reduced. This decrease in effect or impact of feeding is similar to the response we observe in burn patients.

The final question posed by Dr. Levenson and Dr. Clowes, is: What is the hypothalamic lesion which directs the metabolic response to injury?

Our patients shiver in a warm ambient temperature. Our patients ask to be warm. If we put them in the environmental chamber and allow them to control the ambient temperature, they make it warm, much warmer than the comfort temperature selected by normal men.

These patients are more comfortable in a warm environment. The metabolic effect that we provide is not that great, but they are more comfortable. They select higher set ambient temperatures, proportionally to the size of their injury, and they are comfortable with an elevated core and skin temperature.

These are men resting in a warm room with a core temperature of 38 or 39 and a skin temperature of 36, and they are comfortable.

If we study the patients in a cooler environment they will shiver at central and mean skin temperatures above set points for normal man, in that their temperature center has been reset upward.

What causes the adjustment in central temperature set point? Dr. Clowes commented about a tissue injury factor; and, indeed, one of the tissue injury factors being discussed more and more is the prostaglandins. Prostaglandins counteract many of the effects of catecholamines. Our data demonstrate that burn patients have an increased perfusion out to the surface; these patients cannot vasocontrict and insulate like normal men. When they are placed in the cool environment, they cannot prevent their heat from coming to the surface.

Prostoglandins or other hormones of toxins may cause this vasodilatation in the wound and exert additional central effects, such as an effect is on the temperature center.

We have topically anesthetized burn wounds; we have placed spinal anesthesia blocks in people with bilateral leg burns; we have given large doses of aspirin—and none of these techniques or maneuvers reduce the hypermetabolic response to injury in our short term studies. This is truly a reset in the hypothalamus.

Finally, we don't know whether the afferent input from the wound is nervous or whether it's hormonal. We hope to determine this and alter the input or adjust the set point in injured man. This approach will allow great therapeutic potential not only for injured man, but also for countless other metabolic problems.

Chemical Debridement of Burns

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The development of effective, non-toxic (local and systemic) methods for the rapid chemical (enzymatic and non-enzymatic) debridement of third degree burns would dramatically reduce the morbidity and mortality of severely burned patients. Sepsis is still the major cause of death of patients with extensive deep burns. The removal of the devitalized tissue, without damage to unburned skin or skin only partially injured by burning, and in ways which would permit immediate (or very prompt) skin grafting, would lessen substantially the problems of sepsis, speed convalescence and the return of these individuals to society as effective human beings, and would decrease deaths. The usefulness and limitations of surgical excision for patients with extensive third degree burns are discussed. Chemical debridement lends itself to complementary use with surgical excision and has the potential advantage over surgical excision in not requiring anesthesia or a formal surgical operation. The authors' work with the chemical debridement of burns, in particular the use of Bromelain, indicates that this approach will likely achieve clinical usefulness. The experimental studies indicate that rapid controlled debridement, with minimal local and systemic toxicity, is possible, and that effective chemotherapeutic agents may be combined with the Bromelain without either interfering with the actions of the other. The authors believe that rapid (hours) debridement accomplished by the combined use of chemical debriding and chemotherapeutic agents will obviate the possibility of any increase in infection, caused by the use of chemical agents for debridement, as reported for Paraenzyme[21] and Travase.[39,48] It is possible that the short term use of systemic antibiotics begun just before and continued during, and for a short time after, the rapid chemical debridement may prove useful for the prevention of infection, as appears to be the case for abdominal operations of the clean-contaminated and contaminated types.

Patients with intensive deep burns frequently develop serious infections which delay recovery, prolong hospitalization, and are often lethal. Many of these infections originate directly in, and adjacent to, the burned skin area while others may develop initially elsewhere, e.g., the respiratory tract. But these latter infections, too, are generally the consequence of the prolonged presence of the unhealed burned areas with the concomitant metabolic and immunologic disturbances, excluding those patients who suffer severe respiratory tract damage as part of their initial injury and promptly develop tracheobronchitis and/or broncopneumonia. It has long been recognized that the irreparably damaged, ischemic skin, the hallmark of third degree burns, is highly susceptible to infection and this is compounded by the lowered immunologic "defenses" of the severely burned patient. Although the use of local and systemic chemotherapy has lowered deaths from sepis, the incidence of serious infection in burned patients is still frequent, morbidity is still too prolonged, and mortality is still too high. For healing to occur and recovery to take place, the burned skin must separate spontaneously or be removed, the resulting wounds must be grafted, the grafts must take, and the donor sites must heal. As long as dead skin is present, as long as the

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granulating area is unhealed, the possibility of serious infection, local and systemic, exists.

Prompt excision of the burned eschar (tangential[40,41,70] or below the burned tissue,[1,7,9,35,51,63] most often at the musculo-fascial level) and immediate skin grafting (homografting and autografting) have been advocated. Where feasible, this approach is generally successful but when the deep burn is extensive, such excision is a formidable procedure, involving multiple operations, prolonged anesthesia, considerable blood loss and replacement, and carries its own serious complications. In recent years, the use of a CO_2 laser[27,28,53,55,89,90] and the bovie[28,60] for the excision of third degree burns have been introduced. Blood loss can be minimized by these techniques and, at the same time, minimal damage to the underlying tissue results so that immediate grafting can be carried out successfully.

Many physicians concerned with the care of burn patients have recognized and written about the potential usefulness of the early removal of deep burn eschars by chemical means. Artz,[3] for example, pointed this out in his presidential address to the American Burn Association in 1969. However, *no satisfactory method (from the point of view of effectiveness and complications) has been developed up to now.* Evidence for this is the fact that essentially no discussion of this aspect of burn care appears in the chapters on burns in four of the major American textbooks of surgery[19,80,82,93] (each chapter written by a different author) or in a recent book dealing with burns.[4] Another recent book dealing with burns has six lines (out of 262 pages) while another[69] has none dealing with this subject.[59]

From time to time attemtps have been made to use exogenous plant and bacterial proteolytic enzymes applied to the burned areas to "debride" chemically and bloodlessly the deeply burned tissue and to spare the residual viable epithelial elements of partial thickness burns. There have been some bacterial collagenase preparations which have worked rapidly and effectively in certain laboratory animals, but these have not been uniformly effective when applied to human burns. For example, about 12-14 years ago, the Army Research and Development Command and the Walter Reed Army Institute of Research carried out an intensive effort in this regard. The bacterial collagenase preparation worked rapidly and effectively on deep burns of the skins of guinea pigs and rabbits, but was disappointing in a limited trial in man.

There is a preparation of collagenase[*] for human use on the market; it is slow as a debriding agent and not used generally. More recently, a preparation of a proteolytic enzyme from *B. subtilis*[†] has become available for clinical use [22,29,76] but it may have serious limitations as used now by some investigators[39,48] (See Discussion).

None of the major Burn Centers in this country are currently using chemical agents for debridement. However, the fact that such enzymatic preparations have been effective in certain animals makes us believe that the basic idea of chemical or enzymatic debridement is sound. Further, during the last ten years there have been considerable advances in our knowledge of skin and the biochemistry and biophysics of its components, including collagen, the ground substance, and various tissue, bacterial, and plant enzymes. In addition, the *in vitro* and *in vivo* experiments conducted in our laboratory by Levine and us,[53,54,56] the reports of Klein[44,45] with burned pigs, using Bromelain,[‡] have encouraged us to pursue our studies of the chemical debridement of burns.

Our initial observations as reported by Levine *et al.*[53,54,56] showed that Bromelain, a preparation derived from pineapple stems, was more effective *in vitro* in "solubilizing" third degree burn eschar than any other enzymatic preparation we tested, that very rapid debridment (hours) of third degree contact burns in pigs can be accomplished with a single application of 50% Bromelain (buffered to pH 7.4). The healing of partial thickness burns of pigs was not slowed by the Bromelain.

The experiments reported now were conducted to follow up our initial studies in order to devise methods for the safe, rapid chemical debridement of deep burns. It is our view that a combination of local chemotherapeutic agents and effective non-toxic (local and systemic) chemical debriding agents which could be applied early after the injury would improve substantially the care of seriously burned patients. Chemical debridement lends itself to complementary use with surgical excision and has the potential advantage over surgical excision in not requiring anesthesia or a formal surgical operation.

Methods

Pigs were used as one of our species of experimental animals since evidence suggests that the burned skin of the pig may be closer to the burned skin of patients than that of rats, mice, guinea pigs, rabbits, and dogs, animals which have been used largely in earlier studies with chemical debriding agents. Dogs and rats were also used in our studies, especially for skin grafting experiments after debridement, since the subcutaneous tissue of pigs is relatively avascular. Standard contact and hot water burns of known depth and area, both partial thickness and full-thickness, were produced under pentobarbital anesthesia at times supplemented with ether.

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[*] Collagenase, Advance Biofactures Corporation, Lynbrook, New York.

[†] Travase, Flint Laboratories, Division of Travenol Laboratories, Inc., Morton Grove, Illinois 60053.

[‡] Bromelain, Miles Laboratories, Inc., Marschall Division, Elkhart, Indiana 46514; Enzyme Development Corporation, 2 Penn Plaza, New York, N.Y. 10001.

In vitro tests with burned and unburned skin were carried out to assess the effect of the chemical agents and determine conditions of concentration, pH, synergisms and antagonisms. Pieces of burn eschar of fixed dimension and weight were incubated with the chemicals and enzymes under test, generally at 37C in order to speed up the reactions for assay purposes. At varying times, the appearance of the test burn eschar was noted and the nitrogen and hydroxyproline contents of the media and the suspended, fragmented eschar determined as indices of the solubilization and fragmentation of the eschar. Unburned skin was tested similarly simultaneously to detect possible effects of uninjured skin.

Various chemical agents, enzymatic and non-enzymatic, were tested, singly, sequentially, and in combination in different media at controlled pH's and ionic strengths. Appropriate controls, e.g., inactivated enzymes, vehicles, etc. were studied simultaneously. These *in vitro* studies were complemented by *in vivo* studies to assess rates of debridement and possible local and systemic toxicity.

A standardized experimental model devised in our laboratory and reported previously[54] was used for screening debriding activity *in vivo*. Under pentobarbital anesthesia, rows of circular full-thickness burns, each about 20 cm^2 and each about 5 cm from the next burn, were produced on each side of the clipped dorsal skin of female or castrated male white Hampshire-Landrace pigs weighing about 40–50 pounds. The contact burns were created by applying a copper cylindrical block of fixed dimensions at fixed temperatures for predetermined times. In a series of experiments, the time and temperature required to produce the depth of burn desired was determined by sequential biopsies and following the course of healing and sloughing of the burned skin. A temperature of 83–85C for 75 seconds produces a full-thickness burn on the skin of the back of pigs of this size. Standardized partial-thickness burns were produced by shortening the time of contact. Similar burns were produced on dogs.

A number of different chemical agents, both enzymatic and non-enzymatic, were studied in the same pig; the sites used for specific agents were chosen at random. The various enzymes and chemicals were incorporated into various vehicles, e.g., ointment bases, in known concentrations, with and without chemotherapeutic agents.

In other experiments, hot water burns (100C, 6–10 seconds, depending on the size of the rat) were used to produce deep burns on the abdomen or back of rats, involving up to 20–25% body surface. Fixed amounts of the preparations were applied to the burned areas daily (or more often depending on the specific experiment) under a gauze dressing covered with plastic and then held in place by roller gauze, stents or plaster casts.

The rates of debridement of the full-thickness burns were determined and the character of the underlying base assessed grossly and by its ability to accept auto- or homo-full thickness skin grafts, immediately or at various times after debridement. The progression of the debridement, granulation tissue formation and skin grafting was followed by serial clinical, photographic and bacteriologic examinations, including quantitative bacterial counts in some experiments.

Effective debriding agents were also tested on unburned skin and partial thickness burns.

To determine *possible local toxicity* the following types of experiments were done: 1) Effect of the chemical agents with and without chemotherapeutic and antibiotic agents (and appropriate control applications) on reepithelialization of partial thickness burns; and 2) Effect on underlying tissue (a) appearance of the tissue (b) fate of full-thickness skin grafts applied to the area immediately or later after the wound was allowed to granulate.

To assess possible systemic toxicity, 3° burns were made, involving 15–40% of body surface of pigs and 20–25% body surface of rats. The rats received 0.9% sodium chloride, 10% of body weight, intraperitoneally right after burning and 5% glucose in saline by mouth *ad libitum* during the first day after burn. All the animals ate and drank *ad libitum* during the pre- and postburn periods. The rats were fed a commercial rat chow and the pigs commercial pig and dog chows. The agents were applied by the techniques established as most effective by the experiments already described. Full-thickness burns were used; contact for the pigs, produced by repeated contiguous applications of a rectangular copper block 83C for 75 seconds and hot water burns for the rats (100C, 6–10 seconds depending on size of rat). Control animals received similar burns but were treated with the vehicle or inactivated enzyme preparations for the same length of time as the experimental animals; their burn eschars were then excised and thereafter both groups were handled identically. Silver sulfadiazine ointment was applied immediately after debridement and excision under gauze dressings. This was changed 2 days later and reapplied for 3 more days. Thereafter the pigs were left exposed. Body weight hematocrit, plasma total solids, plasma total protein and albumin, blood sugar, blood urea nitrogen, plasma sodium, potassium, chloride, calcium, phosphate, plasma creatinine, CPK, LDH, SGOT, SGPT and alkaline phosphatase were measured[92,93] serially for several weeks; the pig has little if any plasma bilirubin or uric acid. The activity and behavior of the animals were noted.

Bromelain as obtained commercially is a rather crude mixture containing several discrete biological activities not generally associated with a single enzyme. The resolution of each of the component activities into highly purified enzymes was beyond the scope of our investigation. We attempted to partially separate and concentrate the fraction(s) which are most effective in debriding burn eschar. Our guideline was to obtain preferential action against third degree burned skin as opposed to unburned or partial-thickness burned skin.

Commercial Bromelain was mixed with Tris-buffer, pH 7.4, one part Bromelain, to one to two parts buffer. The Bromelain was added slowly to the buffer and stirred gently at room temperature (22–23C) for about 20 minutes. The mixture was centrifuged at 16,000 *g* for 1 hour and the sediment discarded (it was relatively inactive as a debriding agent). The supernatant was decanted and recentifuged at 38,000 *g* for 30 minutes. Again, the supernatant was decanted and the sediment discarded. Aliquots of the supernatant were then introduced into a Sephadex G-100* column or an ion exchange column containing an anion exchange resin† (dimethylaminoethyl exchange groups on a highly purified cellulose powder (DEAE)). For the Sephadex G-100 runs, carried out at room temperature, an amount of supernatant containing about 175 mg N was used; the columns were 36 cm long and 2.6 cm in diameter and Tris-buffer, pH 7.4, was used as the eluting fluid. For the DEAE columns, Bromelain solutions containing about 1300 mg N or 2600 mg N were introduced into columns containing 120 g and 200 g DEAE respectively, the former in a column 38 cm long and 5 cm in diameter, the latter is a column 52 cm long and 5 cm in diameter; sodium citrate, pH 6.0, 0.02 M and 0.5 M were used for the ion exchange column. The eluents were collected sequentially in arbitrary amounts, which were tested for nitrogen by the micro-Kjeldahl methods of Keys[42] and protein content by the biuret method and modifications of Kingsley[43] and Weichselbaum.[97] Carbohydrate content was determined using the anthrone reageant of Dreywood[26] by the method of Scott and Melvin[83] after precipitation of the protein by the Somogyi-Shaffer-Hartman procedure,[84,88] debriding activity against burned and unburned skin, proteolytic activity against casein by the Kunitz technique,[49] amylase activity using the biomedix Amylo-tube set,* lipase activity by the biomedix Delta test.† Certain active collections, as judged by the *in vitro* tests, were frozen, lyophilized and solubilized in Tris-buffer, pH 7.4, in concentrated form and tested *in vivo* with rats with third degree skin burns, using the methods already described.

Sterilization of Bromelain

The solubilized Bromelain and the eluates from the columes were sterilized by passing them through millipore membranes, 0.22 μ.

Results

I. Debridement of Third Degree Burns

A. Pigs. When commercial Bromelain 1200‡ or a further purified preparation of Bromelain† was incorporated in a vanishing cream§ buffered to pH 7.4 with Tris-buffer or in Tris-buffer, the rate of debridement was proportional to the concentration of Bromelain used.

A single application of a 50% concentration of Bromelain to the intact burned area resulted in an obvious debriding effect in 2–4 hours and complete debridement in 12–24 hours. The debriding action by 12–24 hours consisted of some solubilization of the burn eschar and a partially lytic effect at the interface between the burn eschar and the underlying viable tissue so that the eschar could be really dissected off with a throat stick with minimal, and often no, bleeding. The underlying tissue looked undamaged by the Bromelain (Figs. 1, 2). At times there were occasional thrombosed vessels in the underlying subcutaneous layer. (Fig. 3).

When the time of Bromelain was shortened to about 8 hours, the degree of solubilization was less, but dissection with a throat stick could be carried out with relative ease (Fig. 4).

There was little apparent difference in the debriding action of the various preparations of Bromelain, and the results were similar whether the Bromelain was incorporated in the buffered vanishing cream or in the Tris-buffer alone.

Bromelain heated in the Tris-buffer to about 100 C for 3.5 hours lost its debriding action.

The Tris-buffer by itself and the vanishing cream

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* Pharmacia, Uppsala, Sweden.

† Cellex-D, Bio-Rad Laboratories, Richmond, California.

* Princeton biomedix Incorporated, Princeton, New Jersey.

† Miles Laboratories, Inc., Marschall Division, Elkhart, Indiana 46514.

‡ Provided through the courtesy of the Dole Company, Honolulu, Hawaii, 96801, and the Enzyme Development Corporation, 2 Penn Plaza, New York, N.Y. 10001.

§ Pond's Oily Skin Treatment, Cheeseborough Ponds Inc., New York, N.Y. 10017.

FIGS. 1a–c. Large third degree burn of pig. FIG. 1a. Large third degree burn of pig, 1 hour after injury. (Left) dorsal, (center) dorsal-left side and (right) dorsal-right side.

alone hydrated the burn eschar but did not solubilize it when applied for the same times and in the same ways as when the active Bromelain was used (Fig. 5). It is possible to separate the hydrated burn eschar, not acted upon by Bromelain, from the underlying viable tissue by the incision of the eschar and thrusting a throat stick beneath it. However, considerably more force is required than when Bromelain is used. The difference was readily distinguishable when the surgeon did not know before hand which burn eschar had been treated with Bromelain and which had not, e.g. when the period of application was less than 8 hours. For longer applications, the surgeon could tell which eschar had been treated with Bromelain because of the obvious beginning of solubilization, but again there was no question about the dissection being very much easier after Bromelain.

When Bromelain was used in a concentration of 20%, debridement was accomplished in 24–48 hours; concentrations of 10% and 5% Bromelain had progressively slower debriding activity, the latter requiring days.

B. Rats. When Bromelain in a concentration of 50% in buffered vanishing cream or Tris-buffer was applied to hot-water burns of Sprague-Dawley rats the rates of debridement varied depending on: 1) the age and weight of the rat, and thus the thickness and character of the skin; and 2) the location of the burn. The younger the rats, the faster and the more effective the Bromelain. In fact, when the burns were in the backs of the rats, debridement occurred in 4–6 hours in rats weighing 100–150 g (5–7 weeks of age) (Fig. 6), while little or no debridement occurred in 8–10 hours in rats weighing 300–400 g (3–4 months of age). In these experiments the Bromelain was applied for 2–3 hours, then washed off and Bromelain reapplied for another 2–3 hours, etc. In contrast to back burns, when the abdominal skin was burned, debridement was very rapid

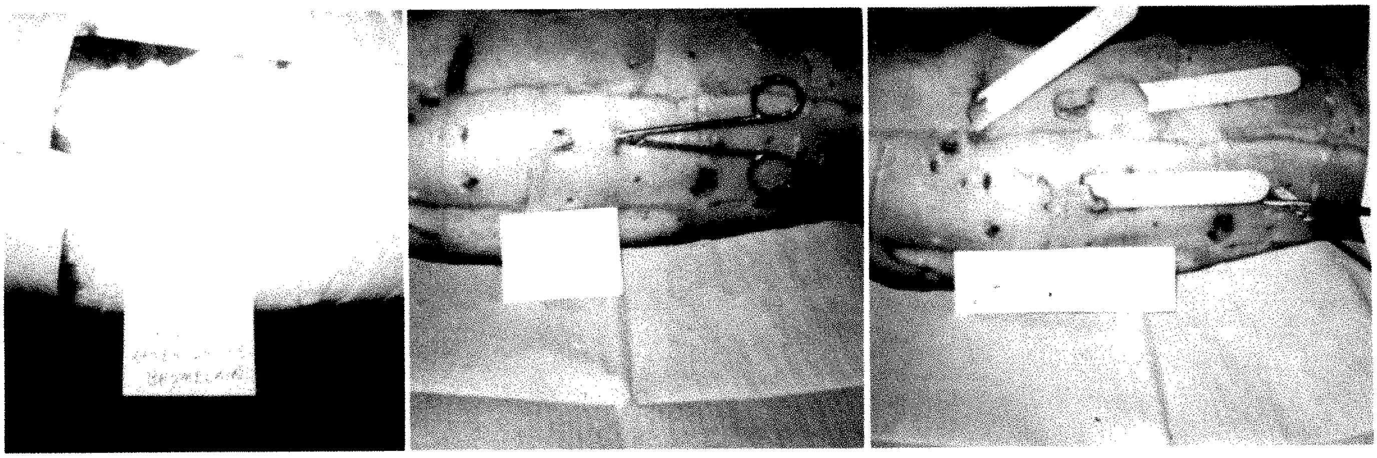

FIG. 1b. The burn was immediately treated with 50% Bromelain in buffered vanishing cream, pH 7.4; single application under dressing. 24 hours later: (left) just before removal of bandage; (center) the intact, but changed, burn eschar easily pierced by a hemostat and, (right) by wooden throat sticks.

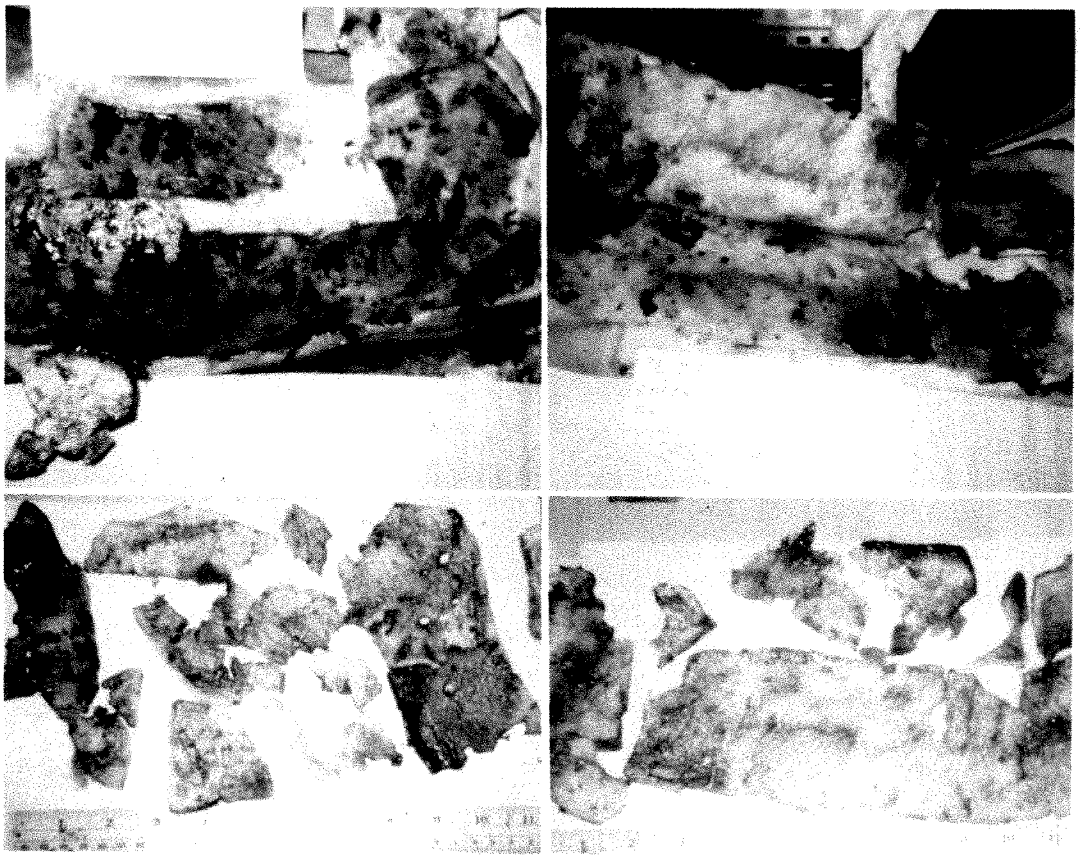

FIG. 1c. Burn eschar readily dissected with throat sticks; appearance of underlying base which is clean and healthy appearing and the dissected burn eschar in large pieces.

in the young rats (2–3 hours) and occurred in the older rats in 3–4 hours (Fig. 7). As in the case of the pigs, the action of Bromelain consisted of some solubilization of the burn and eschar and partial lysis at the interface between the burn eschar and the underlying viable panniculus carnosus so that the eschar could be separated readily by blunt dissection or wiping, the latter requiring proportionately somewhat less time than major solubilization of the eschar.

After debridement of the burn eschar, the underlying tissue appeared healthy. (Figs. 6, 7). Skin grafts, full-thickness homografts from other Sprague-Dawley rats or partial thickness xenografts from pigs, became vascularized (proven by injections of colloidal carbon and gross and microscopic examination) and were then rejected (Figs. 8, 9). The behavior of the grafts was similar to that of xeno- or homografts applied after surgical excision of the burn eschar.

When inbred Fischer rats were used, the skin allografts took very well and persisted indefinitely (Fig. 10), just as occurred when the burn eschars of paired rats were excised surgically and allografted.

C. Dogs. Bromelain, 50% in buffered vanishing cream or Tris-buffer, was effective in debriding third degree contact burns of dogs when applied as a single application and left in place for 18–24 hours. Again, the debridement was characterized by some solubilization of the burn eschar and modification of the interface between the burn eschar and the underlying viable tissue so that removal of 90–100% of the remaining eschar by blunt dissection or wiping was readily accomplished. The base looked healthy, and autogenous skin grafts applied immediately took (Fig. 11) if performed under strict ascepsis.

If the burn eschar is cross-hatched with a scalpel down to, but not into the underlying viable tissue, the rate of debridement is hastened.

II. Effect of Silver Sulfadiazine on Debriding Activity of Bromelain

When Bromelain is mixed with the current commercial preparation of silver suldfadiazine,* its debriding activity was slowed moderately, about 10–20%, when tested in rats and pigs with third degree burns, hot water and contact respectively (Fig. 12).

III. Effect of Bromelain on Healing of Partial Thickness Burns and on Uninjured Skin

Bromelain applied to partial thickness burns of pigs in the concentrations and for the times required for

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* Silvadene, The Marion Laboratories, Kansas City, Missouri 64137.

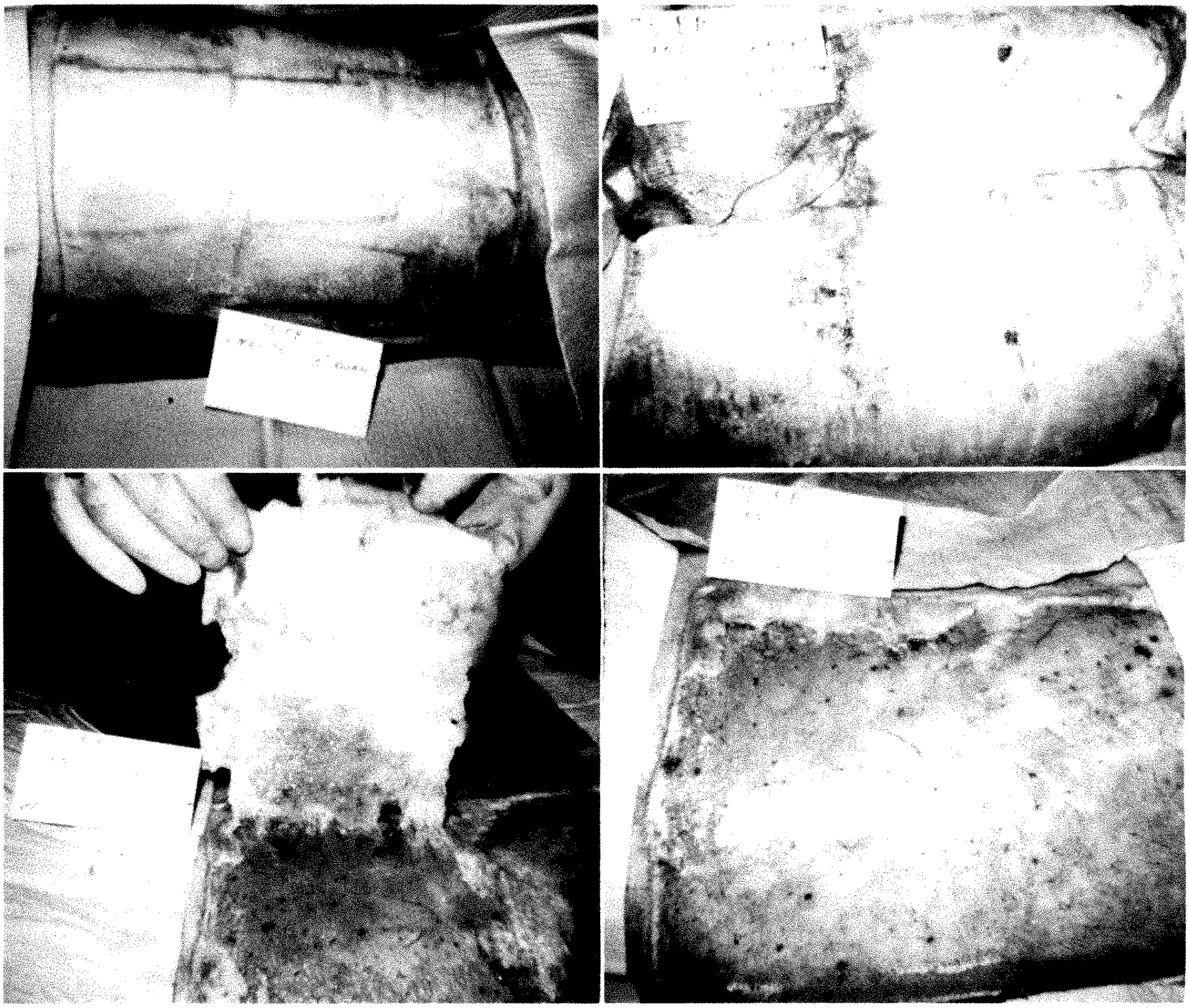


FIG. 2. Upper left, large third degree burn of pig, 1 hour after injury, just before treatment with 50% Bromelain in buffered vanishing cream, pH 7.4. Single application, in place under dressing for 24 hours. The burn eschar was easily removed; upper right, dressing removed, Bromelain cream wiped off; lower left, dissection of eschar with throat sticks; lower right, appearance of underlying tissue, which seems undamaged.

the very rapid debridement of third degree burns does not interfere with epithelization of the partial thickness burns and does not appear to injure unburned skin of pigs, dogs and rats. In fact, 50% Bromelain in Tris-buffer may be applied for as long as 24 hours to partial thickness burns of pigs without slowing re-epithelization.

If 50% Bromelain is applied to unburned skin which has been cut during shaving, irritation and some injury occurs at the cut sites.

IV. Bromelain Debridement of Large Third Degree Burns in Rats and Pigs

A. Rats. Experiments to detect possible systemic toxicity of Bromelain when applied to moderately large third degree burns were conducted with Sprague-Dawley male rats. We found that 50% Bromelain in Tris-buffer or buffered vanishing cream applied promptly after third degree hot water burns involving 20–25% of the skin area of rats (weighing 150–200 g) results in prompt debridement (3–4 hours). Refrigerator stored pig-skin applied to the debrided area became vascularized (proved by I.V. injection of colloidal carbon and gross and microscopic observation) and then undergoes typical "first-set" rejection at 7–10 days (Fig. 9). We used pigskin rather than autogenous skin for these experiments because we did not want to create another wound in these rats. Only 1 of 25 rats so treated died, on about the 10th day. Autopsy revealed some clear

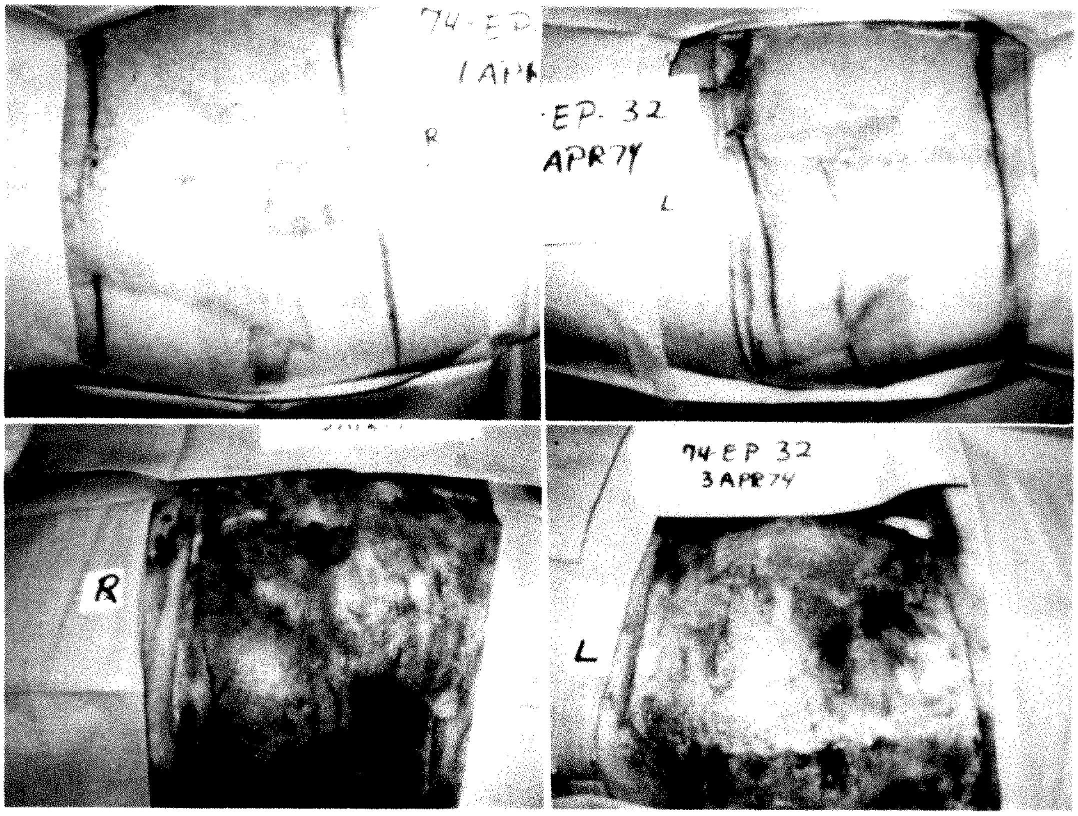


FIG. 3. Large third degree burn of pig showing, upper left, right side and upper right, left side. 50% Bromelain in Tris buffer, pH 7.4 was applied one day after burn and remained on the eschar under dressing for 24 hours. Lower left and right, appearance of underlying undamaged base after dissection with throat stick. Note: thrombosed vessel not debrided.

peritoneal fluid, no petechiae, and no obvious cause of death.

In other experiments, the application of Bromelain was delayed for 24 hours after burning and homografts from other Sprague-Dawley rats rather than xenografts were used. The time for debriding was little different from the preceding experiment. The homografts took well, vacularization was demonstrated by the I.V. injection of colloidal carbon, and the rats survived (Fig. 9).

In a third series of experiments, rats were burned over 20% of their body surface as above. Twenty-four hours later, they were randomly divided into two groups. One group was treated with 50% Bromelain in buffered vanishing cream, the other with the buffered vanishing cream. Several hours later, when debridement by Bromelain was accomplished, the burn eschar of the group treated with vanishing cream only was excised, attempting to stay above the panniculus carnosus, since that was the line of separation of the

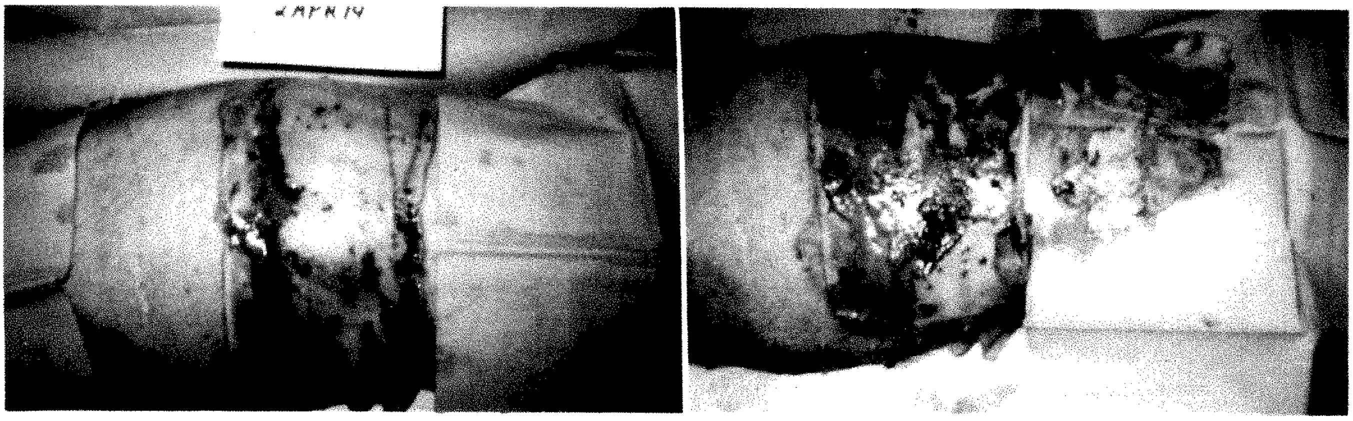


FIG. 4. Twenty-four hours after a third degree burn was inflicted on the side of a pig, 50% Bromelain in buffered vanishing cream, pH 7.4, was applied to the burn and adjacent normal skin and a dressing applied. After 8 hours, no irritation of the normal skin; some solubilization of the burn eschar which could be dissected off with ease with a throat stick. Right, appearance of underlying tissue which seems undamaged.

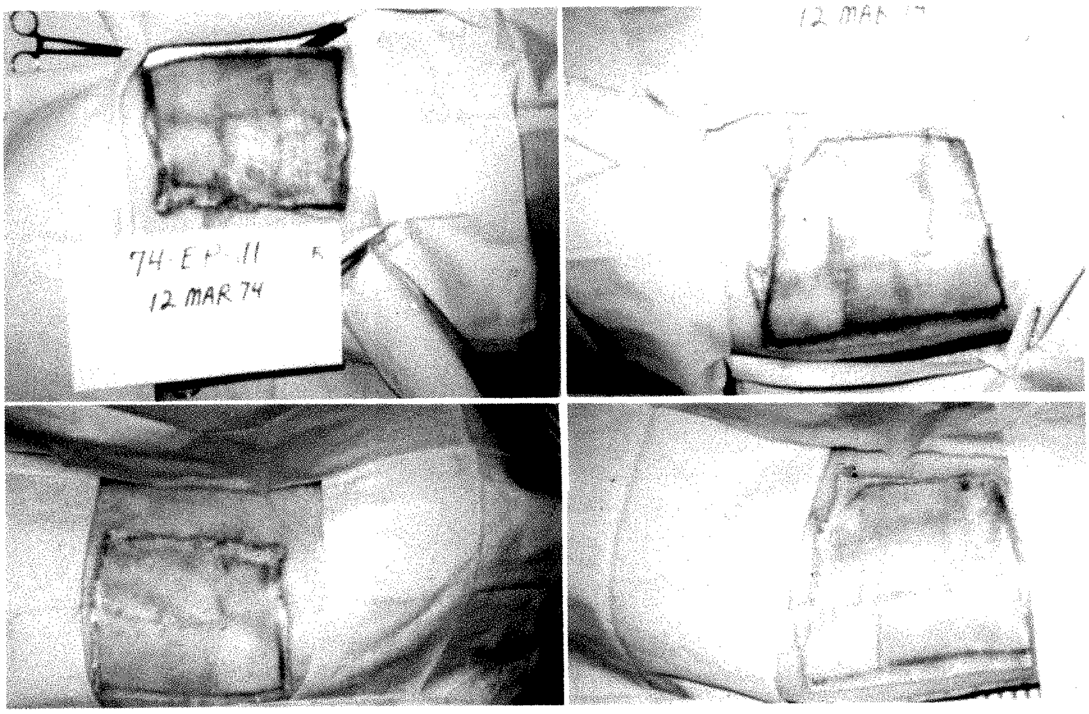


FIG. 5. Effect of buffered vanishing cream pH 7.4 on third degree burns of pigs. Upper left and right, 1 day after injury, ust before application of vanishing cream and dressing. The dressing was removed after 24 hours and the vanishing cream wiped off. Lower eft and right show the ntact, hydrated, but not solubilized, burn eschar.

burn eschar by the Bromelain debridement. Reconstituted lyophilized pig skin was applied to the open wounds of both groups of rats.

There were no differences in behavior, activity, weight gain, hematocrits, plasma total solids and plasma CPK levels of the two groups of rats (Fig. 13, Table 1), the last rising only slightly after burn, in contrast to our findings with pigs.

B. Pigs. In our initial experiment, six pigs were burned deeply (contact) over 30–40% of their body surface. Rapid debridement was accomplished with Bromelain (30–50%) and the wounds covered with lyophilized pig skin or silver sulfadiazine ointment and dressed for 5 days, the dressings being changed at days 2 and 5. Thereafter, the wounds were left exposed to the air. Burned pigs treated with buffered vanishing cream were studied concurrently. The pigs continued to eat, drink and to grow. The debrided areas formed healthy granulation tissue, and there were no blood chemical abnormalities attributable to the chemical debridement (Table 2). Following the burn itself, and unmodified by the chemical debridement, was a very prompt rise in plasma LDH and CPK. The rises in plasma LDH and CPK occur within hours after burning in the pigs and then fell towards normal in about 5–7 days. Plasma SGPT, SGOT and alkaline phosphatase were relatively unchanged.

In another series of experiments young actively growing pigs were divided into two paired groups, each pair being matched according to their body weight and pattern of weight gain. All pigs received third degree contact burns on both flanks, involving 15–20% of body surface. During the pre-burn period, the pigs were housed together, 10–12 in each of two large pens. After the burn injury, the pigs in one experiment were housed together for 7 days and then individually; in another experiment the pigs were housed separately throughout the post-burn period.

After burning, the burned areas of all pigs were left exposed to the air for one day. The burns of one group of pigs in each experiment were then treated in our usual way with 50% Bromelain in buffered vanishing cream, while the other group was treated with the buffered vanishing cream. Eighteen to 24 hours later, the dressings were removed. The areas treated with Bromelain had been partially fragmented and the remaining eschar was removed readily by blunt dissection or wiping. The underlying viable tissue appeared healthy. The areas treated with the vanishing cream alone were intact and were then excised by sharp scalpel dissection. The denuded areas on all pigs were then covered with silver sulfadiazine ointment and a dressing applied. The dressings were changed two days and five days later, following which neither ointments nor dressings were applied. The wounds remained clean. Scabs developed within a short time following exposure of the burn and healthy granulations formed. There was gradual contraction of the wounds, but no epithelization except from the periphery since the burns had destroyed the full-thickness of the skin (Figs. 14, 15).

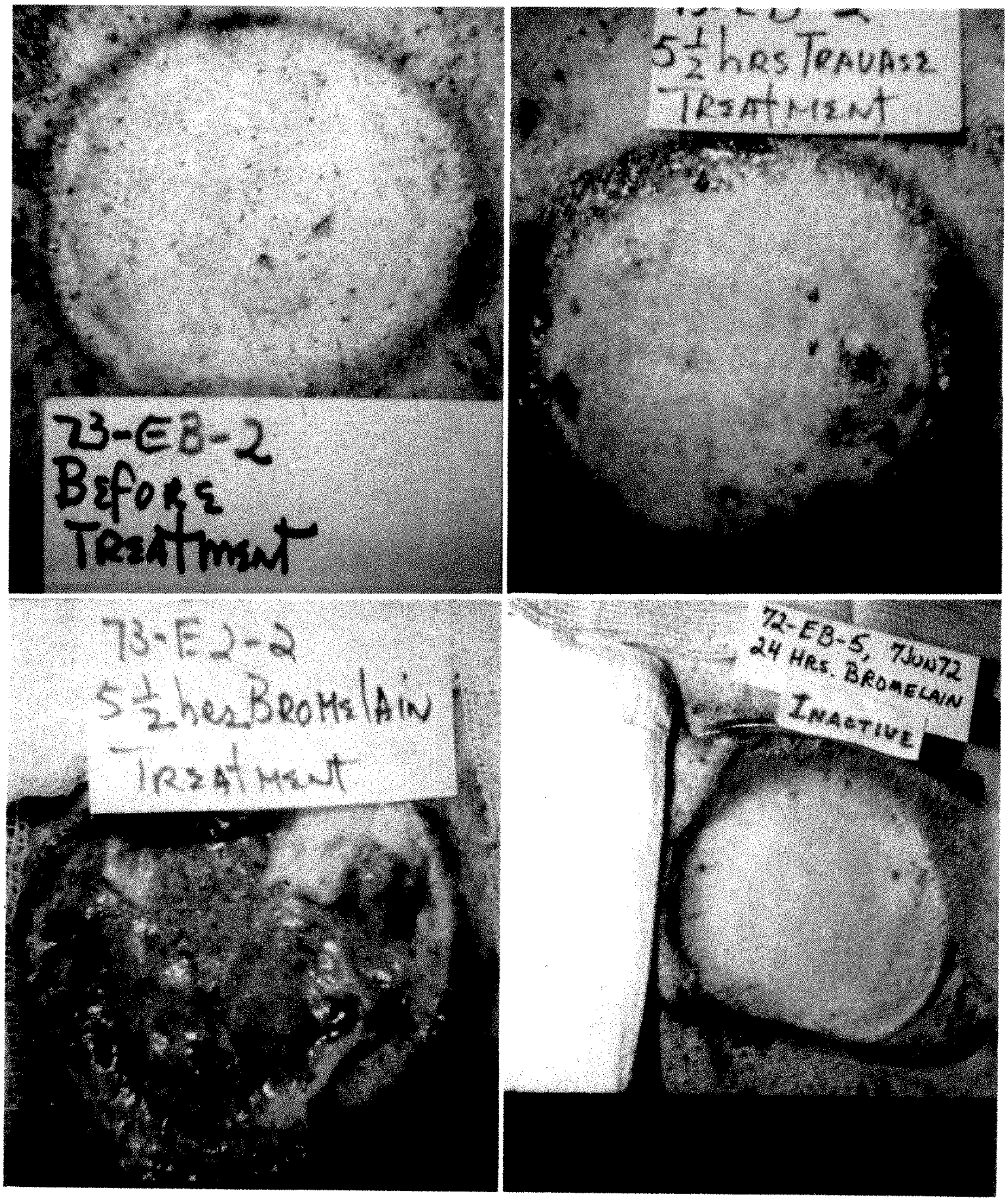
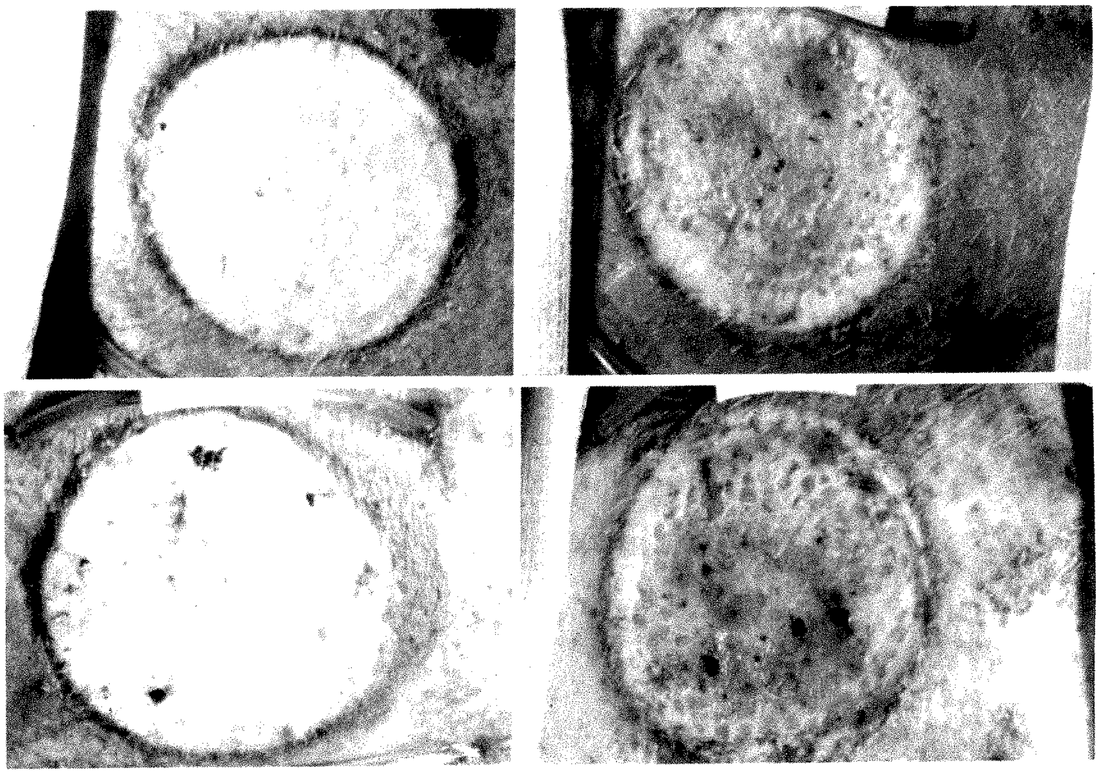


FIG. 6. Effect of 50% Bromelain in buffered vanishing cream, pH 7.4, Travase, and inactivated Bromelain on small (80 cm^2) third degree burns of a pig. Upper left, typical burn area, 24 hours after injury, before treatment; upper right, burn area after 5½ hours of Travase application showing no debridement; lower left, after 5½ hours of 50% Bromelain in buffered vanishing cream, pH 7.4 showing considerable debridement; lower right, after 3½ hours of heat inactivated Bromelain in buffered vanishing cream, pH 7.4, showing no debridement after 24 hours application.

There were no significant differences among the pigs debrided with Bromelain and those in which the burns were treated with buffered vanishing cream and then excised surgically in behavior, activity, apparent food intake (food intake was judged grossly, but not measured), weight gain, hematocrit, plasma total solids, plasma total protein, plasma albumin, sugar, urea nitrogen, sodium, potassium, chloride, calcium, phosphate, creatinine, CPK, LDH, SGOT, SGPT and alkaline phosphatase (Table 2, Figs. 16–18). In both groups, there were prompt rises in plasma CPK, LDH, SGOT and SGPT within 24 hours after burn, before the application of Bromelain or the vanishing cream alone. These rises were especially high (a factor of about 5) for CPK and SGOT. The plasma CPK returned towards normal by the 10th day and there was then a secondary rise 3 weeks following burns. A similar pattern was seen for the plasma SGOT but the secondary rise was much less. Plasma LDH also rose within 24 hours (a factor of 2) and then fell gradually to normal by the 10th post burn day. The rise in plasma SGPT was slightly slower as was its fall, normal levels being reached by day 20. The changes in the plasma enzymes were no different in those pigs subjected to chemical



IG. 7. Effect of various
ncentrations of Brome-
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g cream, pH 7.4, on
nall (80 cm^2) third de-
ee burns of a pig. Up-
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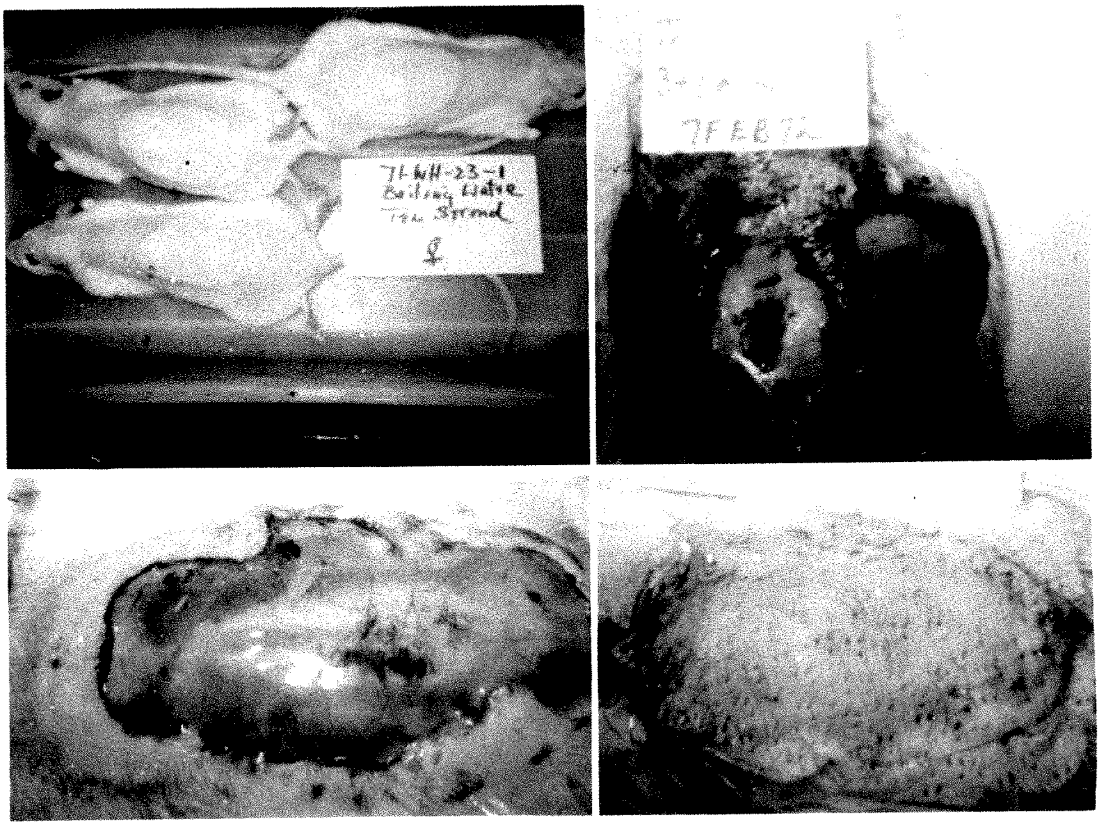

IG. 8. Effect of 50%
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10 seconds in boiling
ater) on the backs of
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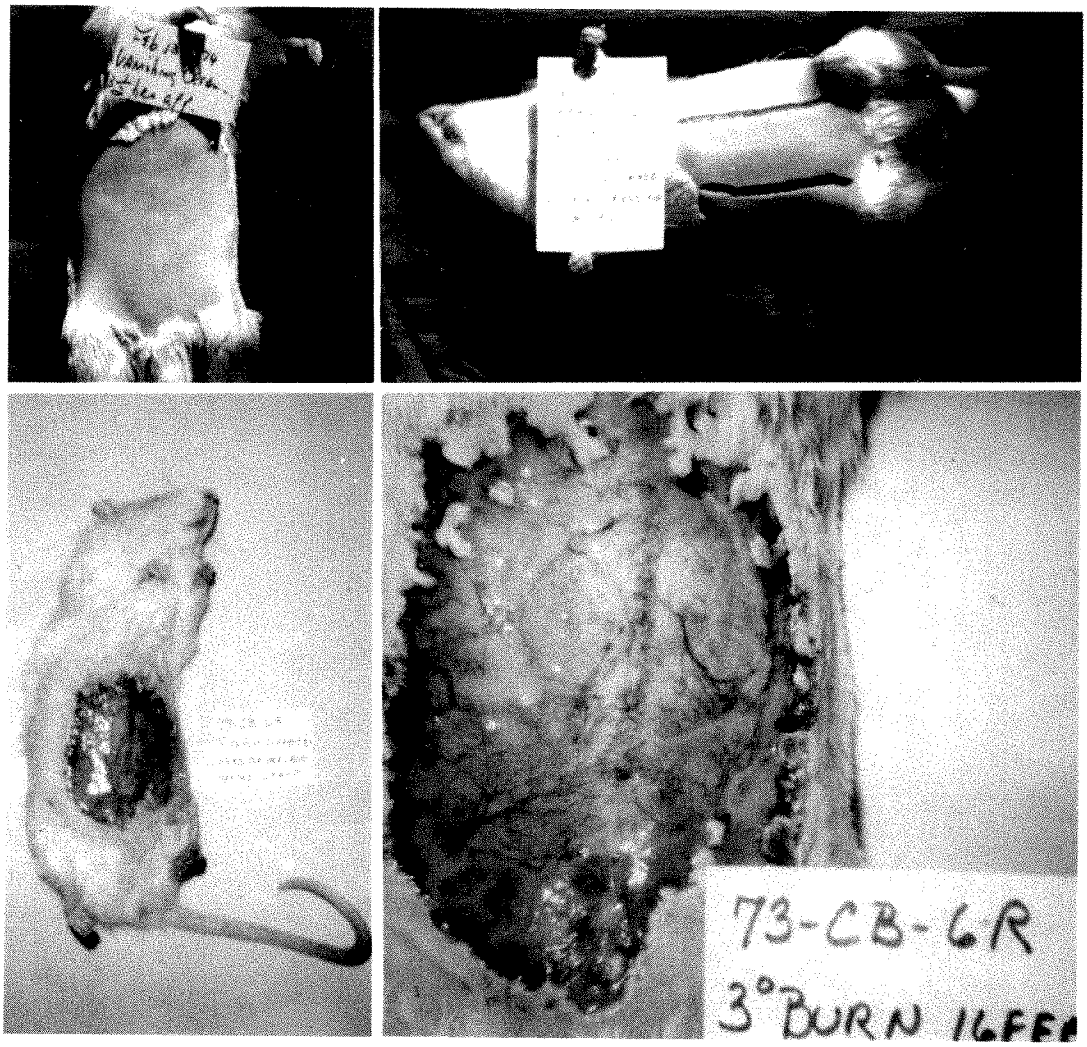


FIG. 9a. Effect of 50% Bromelain in buffered vanishing cream, pH 7.4 and buffered vanishing cream pH 7.4 on third degree burns of the abdominal skin of Fischer rats. Upper left, 3 hour application of vanishing cream; upper right, 3 hour application of vanishing cream and incision of intact eschar; lower left, 3 hour application of 50% Bromelain; lower right, close up of the same area.

debridement with Bromelain than in those pigs treated with vanishing cream and surgical excision.

Control unburned pigs, 2 in number, showed no plasma chemical changes.

Sterilization of Bromelain

Steriliation of Bromelain solutions was accomplished without interfering with its debriding activity. For this, Bromelain was added to the Tris-buffer, pH 7.4, stirred gently for 10 minutes, and then centrifuged for 10 minutes at 2000 rpm. The precipitate was discarded. The supernatant was divided into two equal parts, one of which was not treated further while the other was sterilized by filtering it through a 0.22 μ Millipore membrane. Both solutions showed equal debriding activity. Heating powdered Bromelain for 1–3 hours at 160 C for sterilization destroyed its debriding activity.

Behavior of Current Commercial Bromelain Subjected to Elution from Sephadex G-100 and DEAE Ion Exchange Columns

The currently available commercial Bromelain was partially solubilized in Tris-buffer, pH 7.4, at room temperature (about 22–23 C) so that the nitrogen content of the solubilized fraction was 250–350 mg N/10 ml of buffer. Aliquots of such solutions were introduced in amounts containing about 175 mg N into a Sephadex G-100 column (36 in. long and 2.6 cm in diameter) and eluted with Tris-buffer, pH 7.4, or in amounts of 1300 to 2600 mg N into DEAE ion exchange columns containing 120 and 200 g of the dry resin respectively in columns 38 cm long and 5 cm in diameter and 52 cm long and 5 cm in diameter respectively and eluted with 0.02 M and 0.5 M sodium citrate pH 6.0. The eluates were collected in arbitrary-fractions in each case. The results are shown in Tables 3 and 4 and Figs. 19–22.

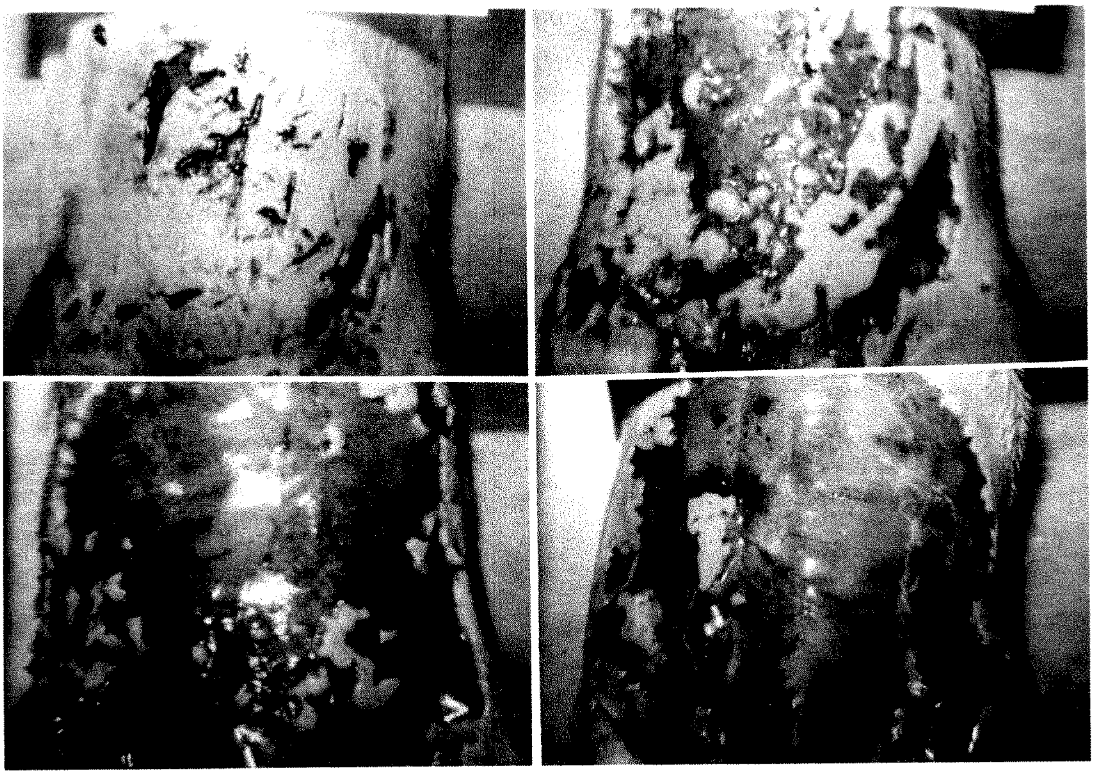


FIG. 9B. Effect of sterile Bromelain solution in Tris buffer, pH 7.4 on third degree burn of the abdominal area of Sprague-Dawley rats. The solution represents the readily soluble portion of a 30% suspension of Bromelain in the Tris buffer. Upper left, ¾ hour application of sterile Bromelain solution showing beginning solubilization of burn eschar; upper right, close up view of 2 hour application of sterile Bromelain solution; lower left, 2½ hour application of sterile Bromelain solution showing increasing solubilization of the burn eschar; lower right, 3 hour application of sterile Bromelain solution showing extensive debridement.

In each case, all the added Bromelain nitrogen was recovered. The majority of the nitrogen eluted from Sephadex G-100 column was in fractions 5–11 and accounted for most of the Bromelain nitrogen which had been introduced into the column. In each fraction, the proteolytic activity aginst casein and the ability to attack burn eschar *in vitro* and *in vivo* (rats) and nitrogen content of the eluate correlated closely. A similar pattern was noted for the DEAE eluates. The bulk of the Bromelain nitrogen introduced into the DEAE columns was recovered in one experiment in fractions 2, 3 and 4 (500 ml eluate); fraction 1, 300 ml contained very little nitrogen (Table 3). In another experiment, the bulk of the Bromelain nitrogen was recovered in fractions 5–10 (100 ml eluate; fractions 1–4 in this run contained 700 ml eluate) (Table 3). These two experiments differed in the amounts of Bromelain solution introduced into the columns and the sizes of the columns; the details about these factors have already been mentioned and are noted in the Table. In each case, there was a high correlation among the nitrogen content of an eluate fraction, its ability to digest casein

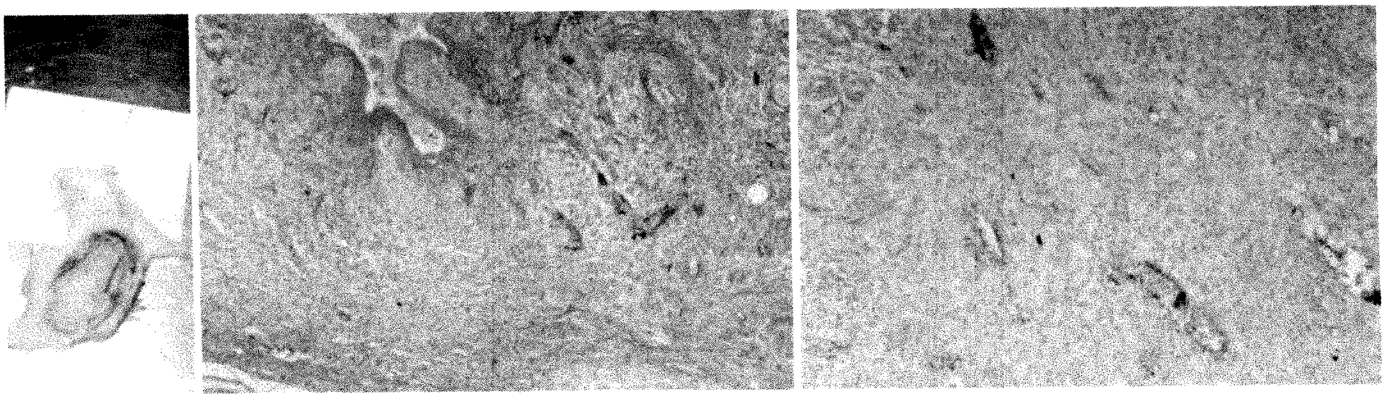


FIG. 10. Effect of Bromelain debridement and immediate xenograft (pig) of third degree burn of a Sprague-Dawley rat. (Left) Eschar was debrided by 50% Bromelain in buffered vanishing cream, pH 7.4 and immediately grafted with porcine skin. Picture was taken four days later. Skin graft completely intact and pink. (Center) Microscopic appearance of pig skin "take." Note colloidal carbon in circulatory system. (Right) Higher magnification of colloidal carbon in blood vessels.

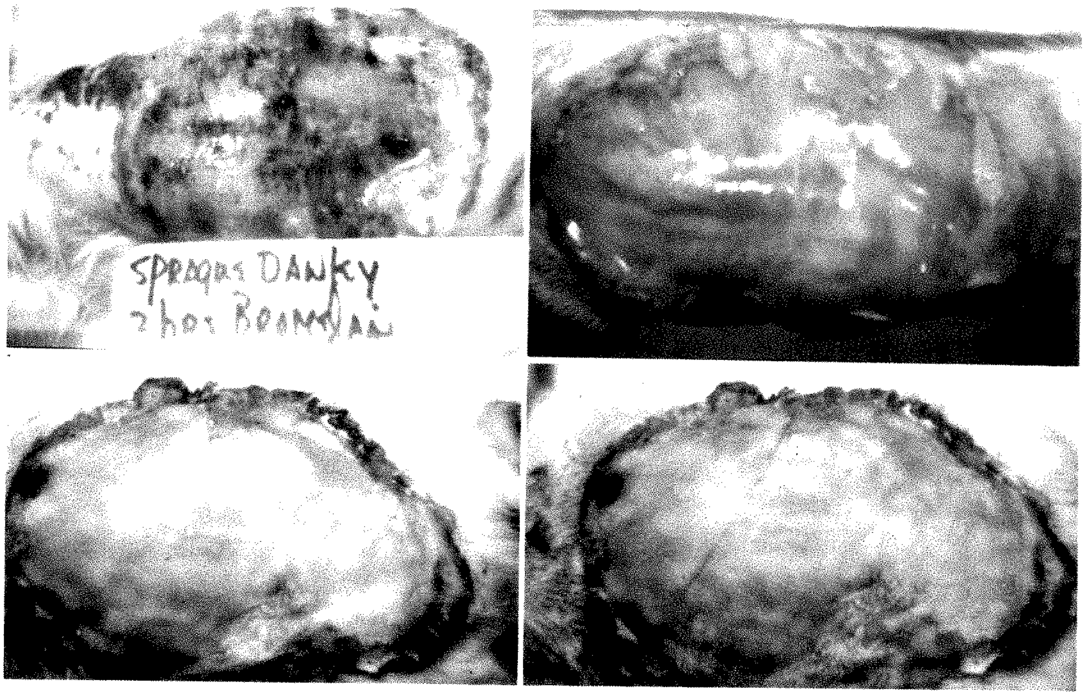


FIG. 11. Effect of 50% Bromelain debridement of third degree burn of Sprague-Dawley rat and immediate homografting of full-thickness skin. Upper left, 2 hour application of 50% Bromelain in buffered vanishing cream, pH 7.4; upper right, burn eschar was detached after 2 hours Bromelain application; lower left, 5 days after debridement and homografting; lower right, colloidal carbon injection showing vascularization of the homograft.

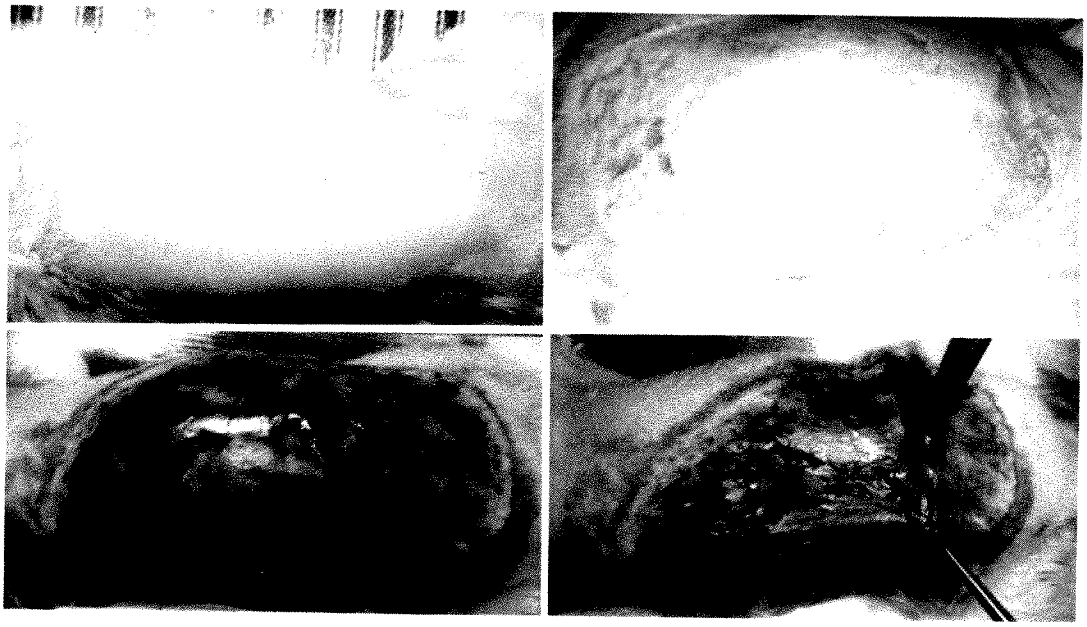
in vitro, and its ability to attack burn eschar *in vitro* and debride burn eschar *in vivo* (rats).

When the various active fractions were "equalized" on the basis of nitrogen content, their proteolytic activities against casein were similar.

The rates of casein digestion relative to different concentrations of nitrogen in the various elution fractions is shown in Fig. 22.

In each case, the action against burned skin *in vitro* was considerably greater than against unburned skin; there was little evidence of any fraction attacking the unburned skin. A similar situation was seen *in vivo* with burned rats.

Neither the commercial Bromelain nor any of the eluate fractions showed lipase activity. On the other hand, the commercial Bromelain and certain of the eluates showed amylase activity; for the DEAE and Sephadex eluates, amylase activity was greatest in those fractions which contained the most nitrogen, had the greatest proteolytic activity against casein, and the



FIGS. 12a–c. Effect of 50% Bromelain debridement, 100 g Fischer inbred rat. FIG. 12A. Upper left, typical third degree burn area on the back of Fischer rat; upper right, after 1 hour application of 50% Bromelain in buffered vanishing cream, pH 7.4; lower left, after 3 hour Bromelain application; lower right, partially solubilized burn eschar being detached.

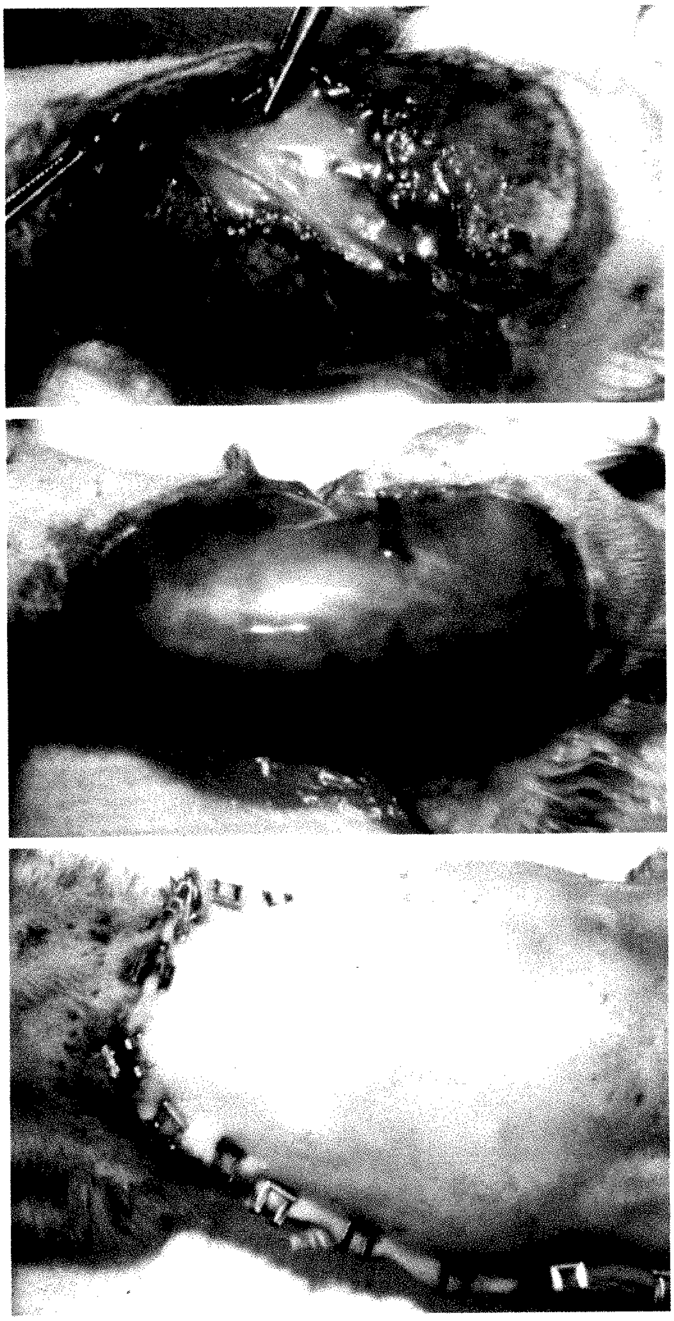


FIG. 12b. (Top) partially solubilized burn echar being detached from panniculus carnosus; (center) appearance of underlying tissue after detachment of burn eschar; (bottom) application of allograft.

greatest debriding activity against burned skin. There was some amylase activity, however, though less, in other fractions (Table 3).

Chemical (Non-Enzymatic Debridement)

Three groups of non-enzymatic chemical compounds were studied *in vitro* and their effects on burned and unburned skin noted: 1) mercaptans which may cleave certain links in proteins (disulfide, ester) and which will also cleave protein-carbohydrate linkage; 2) certain metal ions which cause a weakening of protein fibrillar structure; and 3) compounds which cause a disagregation of mucopolysaccharides.

In the first category, four compounds were studied: a) penicillamine, b) N-acetyl cysteine (Mucomist), c) mercaptoethanol, and d) cysteine ethyl ester.

In the second category were salts of zinc, cobalt and manganese.

In the third category were: a) 8-OH quinoline 5 sulfonate, b) 8-OH quinoline, c) sodium salicylate, d) sodium pyrophosphate, e) sodium tripolyphosphate, f) sodium citrate, and g) sodium EDTA.

The test samples of burned and unburned skin were added to the test chemical solutions and incubated for 24 hours at 37 C. The results are listed in Table 5. Cysteine ethyl ester (0.01–0.1M), 2 mercapto ethanol (0.5–1.0M), N-acetyl cysteine (0.005–0.01M), and penicillamine (0.25–0.5M) demonstrate the desired selective action on burned skin as opposed to unburned skin *in vitro*.

Discussion

Investigative work in the field of chemical debridement of burns has been limited and sporadic. Much of the work has been concerned with proteolytic enzymes produced by various bacteria, particularly *Cl. histolyticum*, and especially with clostridial collagenase. Howes, Mandl and their colleagues demonstrated in several papers[20,36,38,62,64] that three fractions with enzymatic activity could be obtained from the fermentation of *Cl. histolyticum* by ammonium sulfate fractionation: a proteinase, a collagenase, and a peptidase fraction. By *in vitro* tests, the proteinase attacked denatured collagen (as in the eschar of deeply burned skin); the collagenase liquified undenatured collagen and potentiated the action of the proteinase against burn eschar both *in vitro* and *in vivo* when applied on the surface of deep burns. When injected under the eschar, debridement was rapid, but significant damage to the underlying unburned tissue occurred. When applied on the surface, damage to unburned tissue did not occur. The peptidase fraction was capable of removing burn slough when injected under the burn eschar of rabbits, but did not digest burn slough *in vitro;* this was interpreted as meaning that the peptidase fraction activated a tissue enzyme *in vivo*. Their clinical experiences were very limited.

Altemeier and his colleagues[2] also reported on some experiments with three *Cl. histolyticum* proteinase preparations (crude, purified preparation, and a highly purified preparation, as judged by collagenase activity), proteinases from *E. coli*, *Pseudomonas aeruginosa*, and

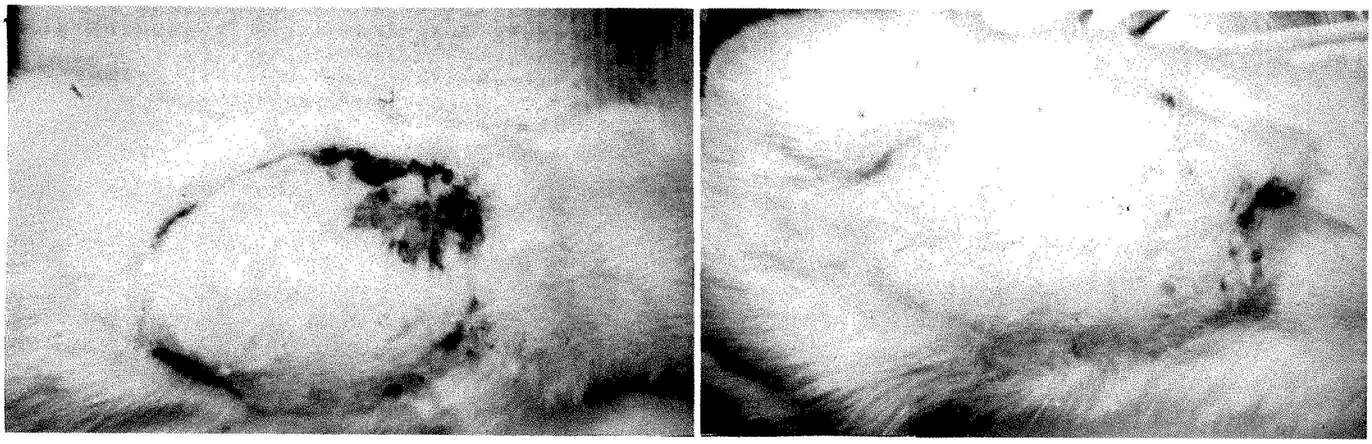


FIG. 12c. Fate of allograft after Bromelain debridement. Left, 2 weeks after Bromelain debridement and full-thickness skin allografting; right, 18 days after Bromelain debridement and full-thickness skin allografting. Excellent take and appearance of the graft.

B. proteus, and a proteinase preparation from a vegetable source. The various preparations were all active (though not identically active) as judged by *in vitro* tests with guinea pig burn eschar, unburned human skin, and by *in vivo* tests with burned guinea pigs. They, too, found subeschar injections led to substantial tissue damage. Also, they found some of the preparations to be antigenic, as did Howes and his co-workers. Altemeier *et al.* mention that their clinical experience was limited to two patients with variable results in terms of debridement.

At the Walter Reed Army Institute of Research (Gochenour, Lowenthal, Webster, Berman and colleagues) an effort was made in the early 1960's to produce, at a pilot plant level, active fractions of *Cl. histolyticum* proteinases for debridement of burns.[6,11,31,95,96] Various fractions were prepared and tested *in vitro* against burned skin and *in vivo* with burned guinea pigs, rabbits, and dogs. As anticipated, different fractions had different activities; collagenase played a major role in debridement of hot water burns (80 C, 15 sec.), while a variety of proteinases readily debrided burns produced by hot oil (200 C, 10 sec.) and contact burns (300 C, 5 sec.). Fourteen days were required for debridement in the dogs with large contact burns (data on controls not given), following which a split-thickness skin graft was applied successfully.

Hamit and Upjohn[32] used one of the fractions prepared at the Walter Reed Army Institute of Research. The fraction of the *Cl. histolyticum* culture filtrate precipitated by 0–22% saturation with ammonium sulfate was used as the source of enzymes; this contained less than 1% of the collagenase in the crude filtrate. Their *in vitro* tests showed that the enzyme preparation digested burned guinea pig skin and muscle more readily than unburned tissues, and that the burned skin was more susceptible to the enzymatic activity than burned muscle. The burns were of the contact type. They found the preparation applied *in vivo* to the burned skin of guinea pigs led to prompt debridement (within 24 hours) but that skin grafts applied immediately did not take. The number of animals involved was small, but they felt their findings were valid. They interpreted this observation as indicating damage to underlying muscle by the enzyme preparation. They pointed out that the subcutaneous tissue in man is fat, not muscle (as in the guinea pig), and how the enzymatic preparation would affect human subcutaneous tissue had not been tested by them.

Very limited trial of some of the Walter Reed Army Institute of Research preparations with burned patients was carried out, but, as far as we know, not reported in the literature. Supposedly, the debriding activity against deep burns in man was insufficient, and some bleeding occurred when applied on areas with exposed blood vessels.

Connell, Rousselot and their associates[12–15,78,79] published a series of papers from 1951–1966. Generally, *in vitro* and *in vivo* experimental studies were carried out, and usually some clinical trials with patients with burns or other wounds with necrotic tissue. They reported experiences with streptokinase and streptodornase.[12] Debricin,* a protease from the latex of the fig trees,[13–15] *B. subtilis* protease, chymopapain, and fungal protease.[78,79] In general, they felt their clinical results were good e.g., with streptokinase and streptodornase, with Debricin, and with the *B. subtilis* protease but it is difficult to interpret their results since the clinical trials were often not sufficiently controlled, i.e., no concurrent observations with inactivated enzymatic preparations or some other suitable controls. They pointed out[78] that

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* Debricin, Johnson and Johnson, New Brunswick, New Jersey 08903.

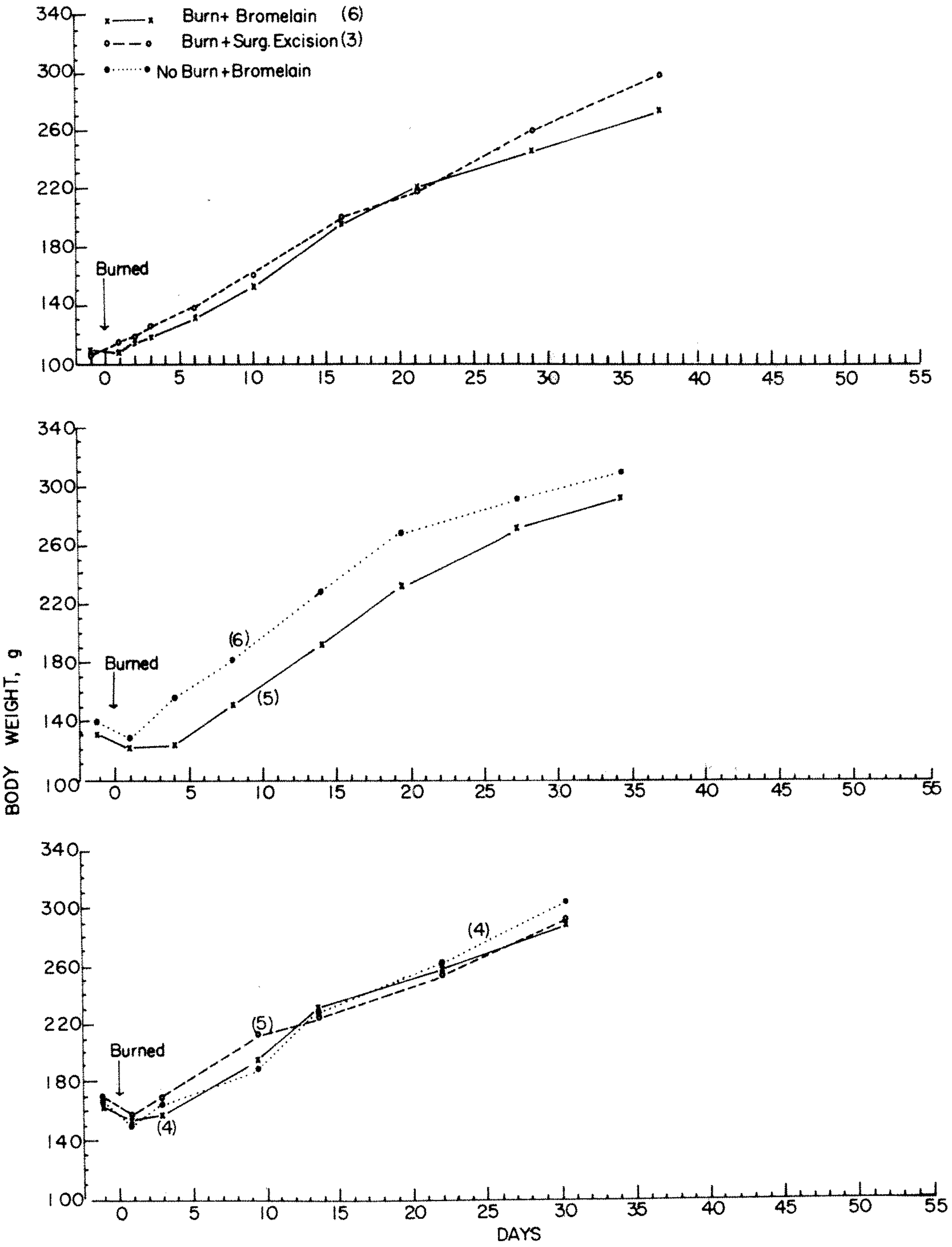


FIG. 13. Effects of 50% Bromelain in buffered vanishing cream, pH 7.4, debridement or surgical excision of large third degree burns of rats on body weight.

a broad spectrum proteolytic enzyme would be required (one possessing collagenolytic activity as well as nonspecific protease activity) because of the complex chemical nature of burned skin.

Mandl and others have advanced the view that certain of the discrepancies reported regarding the debriding activity of collagen represent variations in the preparation and purity of the collagenase enzymes.

Moserova, Zenickova and Holusa[72] used Czechoslovak Collagenase SEVAC (obtained from *Cl. Histolyticum*) which they felt was purer and more active than most collagenases used by others. Third degree contact burns, produced on young piglets, were immediately excised, cubed, and incubated at 24 C or 35 C, in collagenase solutions in a borate buffer, pH 7.4. The amount of collagenase used was equivalent to 1–2% of the dry weight of the burned skin cube. Burned skin dissolved in 48–96 hours, depending on the concentration of collageneas and incubating temperature, while unburned skin treated comparably retained its shape and consistency, though there was histologic evidence of changes, but whether these were due to collagenase or

TABLE 1. *Effect of Bromelain on Body Weight, Hematocrit and Plasma Total Solids on Burned S-D Rats*

Exp. no.	Days after Bromelain			Body Weight g	Hematocrit, %	Plasma Total Solids, G/100 ml
I	Before Burn	Bromelain	(6)*	109 ± 4	46 ± 1.1	7.0 ± 0.2
		Surgical Excision	(3)	104 ± 3	48 ± 0.9	6.7 ± 0.1
	2 Days	Bromelain		115 ± 3	38 ± 1.4	7.2 ± 0.2
		Surgical Excision		125 ± 3	36 ± 0.9	6.6 ± 0.1
	6 Days	Bromelain		137 ± 5	42 ± 0.7	6.8 ± 0.1
		Surgical Excision		138 ± 5	43 ± 0.3	6.7 ± 0
	10 Days	Bromelain		151 ± 3	45 ± 0.7	7.4 ± 0.2
		Surgical Excision		163 ± 5	44 ± 2.1	7.7 ± 0.4
	16 Days	Bromelain		193 ± 3	46 ± 1.0	7.3 ± 0.1
		Surgical Excision		194 ± 8	45 ± 1.9	7.4 ± 0.1
	21 Days	Bromelain		210 ± 11	—	—
		Surgical Excision		209 ± 8	—	—
	29 Days	Bromelain		242 ± 16	—	—
		Surgical Excision		261 ± 11	—	—
II	Before Burn	Bromelain	(5)	131 ± 2	44 ± 0.6	6.8 ± 0.1
		No Burn + Bromelain	(6)	140 ± 2	44 ± 0.6	6.8 ± 0.1
	1 Day	Bromelain		121 ± 2	36 ± 1.1	6.5 ± 0.2
		No Burn + Bromelain		129 ± 2	40 ± 1.5	6.4 ± 0.1
	4 Days	Bromelain		122 ± 7	42 ± 0.6	6.8 ± 0.1
		No Burn + Bromelain		159 ± 2	46 ± 0.4	8.0 ± 0.1
	8 Days	Bromelain		152 ± 3	44 ± 1.0	6.9 ± 0.1
		No Burn + Bromelain		188 ± 5	46 ± 0.3	8.0 ± 0.2
	14 Days	Bromelain		195 ± 5	42 ± 0.9	7.3 ± 0.2
		No Burn + Bromelain		236 ± 7	45 ± 0.8	7.5 ± 0.1
	19 Days	Bromelain		221 ± 4	—	—
		No Burn + Bromelain		260 ± 8	—	—
	27 Days	Bromelain		261 ± 7	—	—
		No Burn + Bromelain		282 ± 12	—	—
III	Before Burn	Bromelain	(4)	165 ± 3	44 ± 0.8	6.8 ± 0.1
		Surg. Excision	(5)	169 ± 2	49 ± 0.9	6.9 ± 0.1
		No Burn + Bromelain	(4)	167 ± 1	46 ± 1.6	6.8 ± 0.3
	1 Day	Bromelain		152 ± 4	35 ± 1.7	6.7 ± 0.1
		Surg. Excision		159 ± 7	37 ± 1.0	7.1 ± 0.2
		No Burn + Bromelain		150 ± 2	43 ± 0.9	7.5 ± 0.1
	3 Days	Bromelain		155 ± 8	41 ± 0.9	7.0 ± 0.1
		Surg. Excision		168 ± 7	38 ± 0.9	7.1 ± 0.1
		No Burn + Bromelain		170 ± 2	43 ± 1.7	7.3 ± 0.1
	9 Days	Bromelain		193 ± 7	45 ± 1.2	7.1 ± 0.1
		Surg. Excision		219 ± 9	42 ± 1.2	7.1 ± 0.3
		No Burn + Bromelain		181 ± 5	46 ± 1.7	7.8 ± 0.1
		Bromelain		227 ± 8	—	—
	14 Days	Surg. Excision		223 ± 11	—	—
		No Burn + Bromelain		225 ± 4	—	—
	22 Days	Bromelain		260 ± 6	—	—
		Surg. Excision		246 ± 15		
		No Burn + Bromelain		268 ± 2		

* Number of rats.

spontaneous autolysis was unclear to them. Histologic observations indicated that when skin with partial thickness burn was incubated with the collagenase, the heat-damaged upper layers were affected principly by the enzymatic action.

The most active preparation was used by them *in vivo* on small third degree burns on the backs of pigs; control areas were treated with the vehicle (Synderham ointment) only in which the collagenase was incorporated.

> . . . After 24 hours, excision for histological examination were taken from both burned areas. On the area treated with collagenase, the whole dermal layer was absent except for a few thin, negligible islets of the deep dermal layer. On the control area a full thickness burn was found, upper layers of the dermis showing homogenization the deep layer of thermally damaged collagen retaining partly its structure. There were no changes whatever found on thermally uninjured skin, treated for 24 hours with Synderman ointment containing the enzyme.

Koehnlein and Lemperle[47] studied the debriding effects of collagenase, collagenase with chloramphenicol, fibrinolysin (the vehicles in which the various enzyme preparations were applied is not stated in the report), carbolic acid (0.35% in cod liver oil), pyruvic acid (10%

TABLE 2.

Pig Number	Post Burn	T. P. gms %	Alb. gms %	Ca mg %	PO_4 mg %	Creat mg %	Alk. P mIU/ml	CPK mIU/ml	LDH mIU/ml	GPT mIU/ml	GOT mIU/ml
73EB12	0	6.8	0.8	9.1	5.9	1.1	41	453	298	8	24
	1	6.8	0.9	7.3	6.7	1.4	48	12,600	1,790 H	31	175
	2	7.0	0.6	9.6	6.7	1.3	60	>5,000	840	64	264
	6	4.5	0.9	8.7	7.3	1.1	29	465	547	41	187
73EB8	0	6.1	1.6	10.4	7.8	1.2	59	312	213	23	15
	1	6.0	1.6	10.0	7.2	1.3	59	7,600	561	40	121
	2	5.6	1.3	9.5	6.6	1.0	42	4,600	511	50	67
74EP3	0	5.5	3.1	9.8	7.8	1.0	201	162	276	25	34
	1	5.2	2.5	9.3	8.3	0.9	175	535	393	21	46
	2	5.3	2.6	8.1	7.0	0.8	120	460	333	27	44
	7	5.2	2.5	9.1	7.8	0.8	87	168	265	18	25
	17	5.3	2.4	8.3	6.9	0.8	89	413	303	8	40
	24	5.4	2.3	9.5	6.8	1.0	94	204	207	4	16
	36	5.3	2.3	8.2	6.8	0.5	102	366	279	17	12
74EP19	0	5.1	2.4	9.9	7.7	1.1	178	199	370	2	52
	1	5.3	2.2	9.5	8.5	0.9	162	619	695 H	16	123
	2	5.6	2.7	8.8	6.6	0.9	107	534	454	21	81
	4	5.3	2.1	9.2	5.8	0.8	80	292	352	7	45
	7	5.5	2.4	9.1	7.7	0.9	84	161	345	4	29
	17	5.6	1.9	8.5	7.4	0.9	113	496	505 H	15	63
	24	5.8	2.4	9.4	6.7	1.1	112	214	259	6	33
	36	6.0	2.5	9.3	7.9	1.1	123	2180	750	11	30
74EP7	0	5.8	2.8	9.1	6.5	0.9	111	547	588	23	105
	1	6.2	2.9	10.0	7.5	0.8	98	567	583	30	120
	4	5.8	2.4	9.4	6.0	0.8	62	522	759	27	101
	7	5.9	2.4	9.3	7.0	1.0	61	70	424	24	42
	14	5.8	2.1	9.2	7.0	0.7	152	82	345	33	32
	24	6.9	2.5	9.7	6.8	1.0	89	109	352	29	32
	30	7.4	2.8	10.5	7.0	1.1	93	185	370	27	34
	43	6.9	3.0	8.8	6.4	1.3	112	196	199	14	11
74EP11	0	5.5	3.1	10.5	8.2	1.0	128	250	422	31	43
	1	5.4	2.7	10.0	7.2	1.0	117	587	397	30	60
	2	5.3	2.4	9.3	6.4	0.9	103	657	625 H	51	128
	4	5.5	2.5	10.0	7.0	1.0	80	503	452	48	71
	7	5.3	2.5	9.0	6.8	1.1	67	217	328	27	37
	14	4.6	2.1	7.9	5.9	1.1	73	144	338	24	34
	24	5.8	2.5	9.4	6.9	1.1	77	211	366	24	26
	30	6.0	2.7	10.6	8.1	1.4	83	263	400	28	29
	43	5.4	2.6	9.1	7.4	1.4	107	876	217	7	19
74EP10	0	5.3	2.1	9.1	7.6	0.8	189	151	465	20	65
	1	5.7	2.4	9.9	8.0	0.8	176	610	569	46	158
	2	5.2	2.2	8.9	7.9	0.8	126	613	820 H	41	226
	3	4.9	1.7	8.2	6.4	0.7	102	570	545	60	234
	6	5.6	1.6	9.0	8.2	0.8	100	248	564	50	94
	13	5.5	1.9	9.6	7.1	0.7	182	85	374	31	33
	23	6.4	1.8	9.0	7.3	0.7	112	395	330	23	57
	29	6.9	2.6	10.2	7.4	1.0	146	361	413 H	28	40
	42	6.2	2.7	9.1	7.2	1.1	181	867	318	18	53
74EP6	0	4.8	2.1	9.6	7.5	0.9	173	53	373	29	28
	1	5.1	2.3	9.7	7.5	0.7	159	529	391	35	73
	2	5.5	2.3	8.9	6.9	0.8	119	520	597 H	45	112
	3	5.1	2.0	8.7	6.5	0.7	79	546	485	56	171
	6	4.9	1.7	8.6	6.4	0.7	59	79	409	34	41
	13	5.1	1.7	9.3	6.3	1.0	109	71	451 H	30	40
	23	5.4	1.2	8.1	7.8	1.2	84	306	414	15	51
	29	5.7	2.0	9.1	6.5	0.8	78	157	345	19	25
	42	5.8	2.3	8.9	7.3	1.0	99	551	251	18	23
74EP8	0	5.2	2.6	9.6	7.5	0.5	117	155	310	18	26
	1	5.4	2.4	10.1	7.6	0.6	110	490	585	22	80
	2	5.1	2.3	9.4	8.0	0.9	103	385	640	46	108
	4	5.5	2.4	9.5	7.3	0.7	85	105	413	28	114
	7	5.3	2.1	9.7	7.1	1.1	88	165	328	22	56
	17	5.4	2.5	9.3	7.5	0.9	78	225	362	19	28
	24	5.6	2.7	9.2	7.2	1.0	80	210	280	12	19
74EP12	0	5.5	2.4	10.0	7.3	0.9	128	245	255	8	32
	1	5.3	2.5	9.3	6.9	0.6	135	510	418	19	50
	2	4.6	2.9	8.8	6.4	0.8	114	665	845 H	26	58
	4	5.1	2.1	9.2	6.9	0.8	90	242	322	26	30

TABLE 2. (*Continued*)

	7	5.5	2.8	9.5	7.2	0.6	63	156	352	16	38
	17	5.3	3.1	9.3	7.7	1.0	72	116	210	18	16
	24	5.6	3.0	9.5	7.3	0.7	75	390	200	9	14
74EP34	0	4.5	2.3	9.5	6.1	1.1	153	205	88	16	17
	7	5.1	2.9	10.1	6.0	1.3	95	413	112	12	15
	15	6.4	3.8	10.3	7.2	1.3	86	571	155	24	24
74EP37	0	4.6	2.2	9.5	6.0	0.8	155	217	96	24	26
	7	5.4	3.0	9.9	6.7	1.2	126	282	84	19	15
	15	6.1	3.3	9.8	6.8	1.1	104	325	112	29	22

T. P —Total Protein
Alb —Albumin
Ca —Calcium
PO_4 —Phosphorus
Creat—Creatinine
H —Hemolyzed

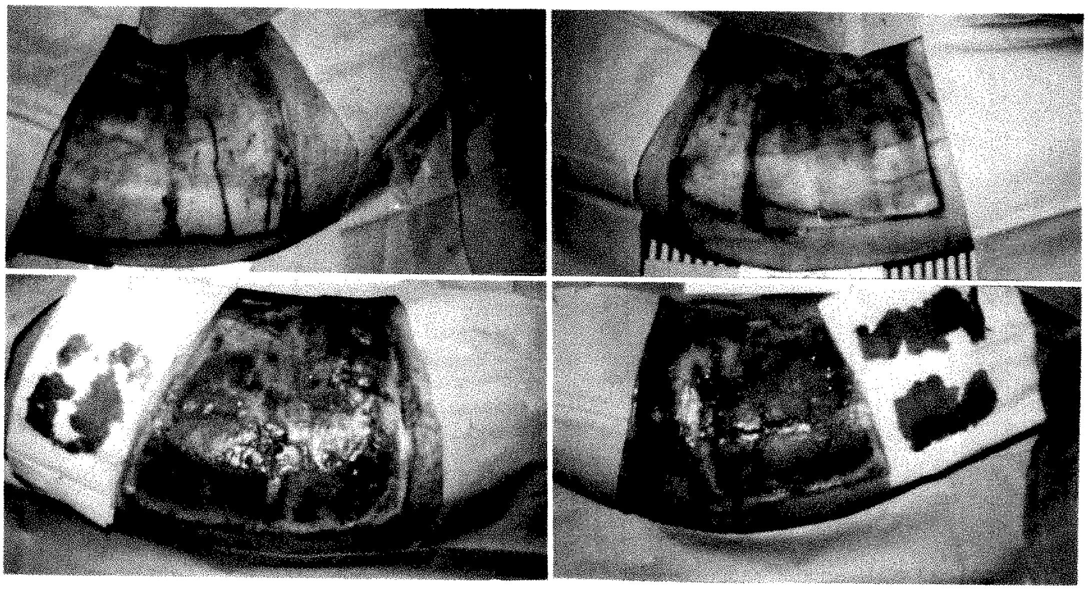
Alk. P —Alkaline phosphatase
CPK —Creatine phosphokinase
LDH —Lactic Dehydrogenase
GPT —Glutamic pyruvic transaminase
GOT —Glutamic-oxaloacetic transaminase
mIU/ml—Milli International Units/ml

in starch paste, pH 1.9), normal saline, and dry dressings on third degree contact burns on the backs of rats weighing about 200 g. The various preparations were applied immediately after burning under dressings (details not given) and then each 24 hours thereafter until complete sloughing of the eschar occurred. Separation of the ecshar for the control dry dressing group was 9–15 days and for the saline group 8–12 days. In contrast, separation for the collagenase treated burns was 1–3 days. When chloramphenicol was added to the collagenase, debridement was slower, 2–6 days, but still much faster than the controls. The time of eschar separation for the fibrinolysin treated rats was 2–5 days, for the 0.35% carbolic acid group 4–7 days, and for the 10% pyruvic acid group 5–8 days. They state that . . . "In the meantime we have used collagenase in 19 patients with 3rd degree burns with very satisfactory results," but no details are given.

A Symposium on Collagenase, which included some papers on the use of collagenase in burns, was held at Columbia University in 1970.[65] The presentations suggested some clinical usefulness. As already mentioned, there is a preparation of collagenase for human use on the market in the U.S.A., but it is slow as a debriding agent and is not used generally for the treatment of burned patients.

Douglas, Ferriday, and Gaughran[24,25] in 1958 reported some *in vitro* and *in vivo* studies with burned guinea pigs and found that the purified fig latex protease (Debricin) was substantially more effective as a debriding agent than trypsin, papain, streptokinase-streptodornase, and papain-chlorophyll-urea. Their work laid the basis for that with Debricin by Connell, Rousselot and their colleagues, already described.

Papain has been used frequently in experimental studies and for clinical use[8,25,68] with inconstant results. Miller[68] found that a combination of papain, urea and cysteine was more effective than papain alone in digesting collagen of cadaver skin (unburned). He ascribed this to a denaturation of collagen by urea and the pro-



FIGS. 14a–c. Effect of 50% Bromelain in buffered vanishing cream, pH 7.4 on large third degree burn of pig. FIG. 14a. Upper, left and right, typical third degree burn of pig, 1 day after injury; lower left and right; appearance following a single application of 50% Bromelain for 24 hours; considerable solubilization of the burn eschar, on both sides of pig; the remaining eschar could be dissected off readily with a throat stick.

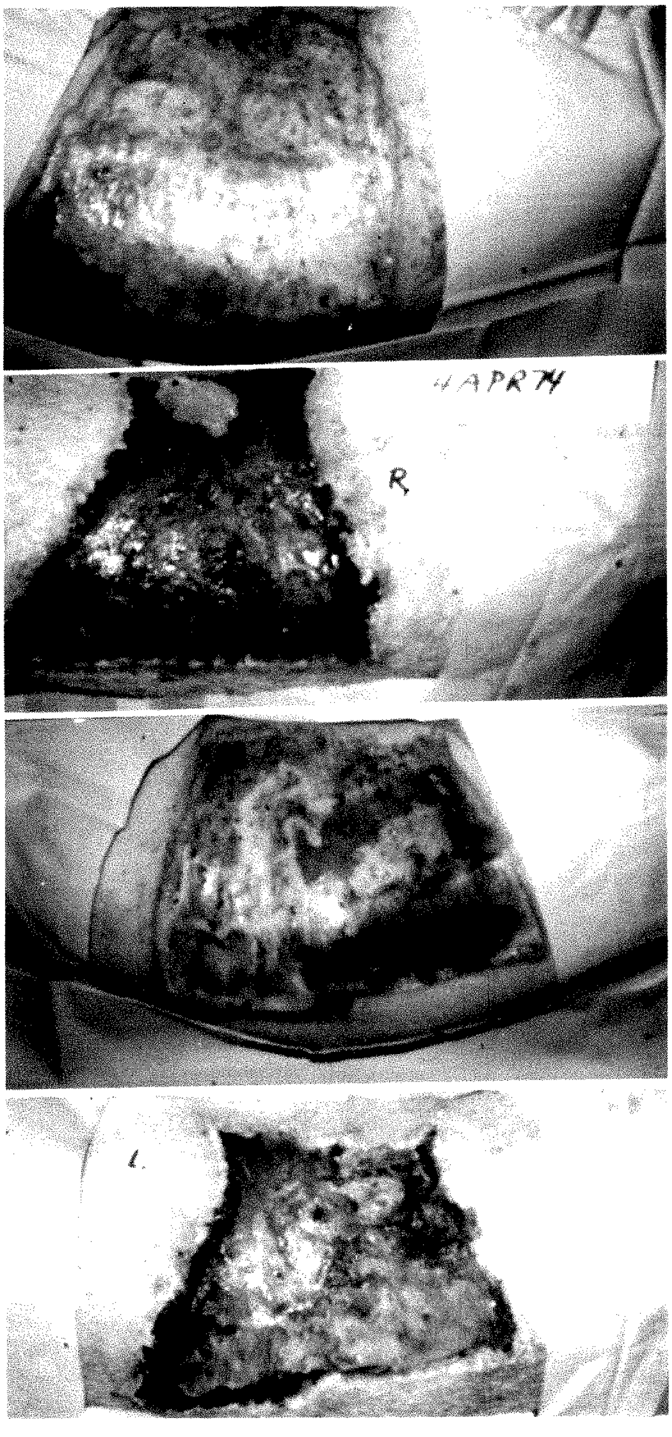


FIG. 14b. First and third, single application of 50% Bromelain for 24 hours, appearance of base after ready dissection of remaining burn eschar; second and fourth, 20 days after Bromelain debridement.

vision of SH groups by cystein. (We think this concept is basically sound; amplification of this appears later in this paper).

Papain-urea-chlorophyll ointment was used clinically by Burke and Golden[8] in 27 patients, one of which was burned. They conclude that the preparation was an effective, safe debriding agent, but the data can not be evaluated satisfactorily because of the lack of adequate controls.

A similar criticism can be directed towards the report of Liljedahl and Backdahl[58] who used Ethizyme* (a proteolytic enzyme preparation from the liquid of the tropical maya fruit) on the burns of 7 patients. They were convinced that debridement was significantly hastened by the enzyme preparation and found that skin grafts applied 2 days or so after debridement was complete took very well. We have not found follow up reports by these authors.

Shelby *et al.*[85] used Viokase,† a pancreatic preparation with proteolytic, amylase and lipase activity, in 125 patients with a variety of wounds with some necrotic tissue. Nineteen of the patients had second and third degree burns. They felt the Viokase was a "valuable adjuvant in the management of infected wounds," but again there was no adequate controls.

Dimick and Sullivan[21] reported in 1966, five severely burned patients who developed bacteremias (3 of whom developed fatal septicemias) 8–12 hours after the application of Parenzyme‡ ointment, which contains trypsin, chymotrypsin and 9 aminoacridine. The enzyme preparation was applied for the first time 6–20 days after burn in these patients. Dimick and Sullivan interpret these observations as indicating . . . "This therapy appeared to facilitate, bacterial proliferation and seeding of the bloodstream." Their data are difficult to interpret since bacteremia and septicemia occur in such patients without enzyme treatment. However, the coincidence of enzyme application and bacteremias 8–12 hours later in the five patients is striking. We have not found other reports in which this enzyme preparation has been used.

Travase,§ a commercial preparation of proteolytic enzyme(s) prepared from *B. subtilis* is currently under evaluation in the United States for the treatment of burns in patients. Laboratory investigations by Silverstein *et al.*[87] showed that an experimental proteolytic enzyme preparation obtained from *B. subtilis* was very effective in vitro against burned skin. McCann, Tsuru and Yasunobu[67] had reported previously on some of the biochemical characteristics of *B. subtilis* neutral proteinase and found it to be a zinc enzyme. The commercial preparation, sterilized by gamma radiation, is homogenized into a hydrophobic ointment base and is stable for 10 months when refrigerated at 2–10 C. It appears to be non-injurious for unburned skin and to

---

* Ethizyme, Ethicon (Vitrum).

† Viokase, Viobin Corporation, Monticello, Illinois 61856.

‡ Parenzyme, National Drug Company, Division of Richardson-Merrell, Inc., Philadelphia, Pa.

§ Travase, Flint Laboratories, Division of Travenol Laboratories, Inc., Morton Grove, Ill. 60053.

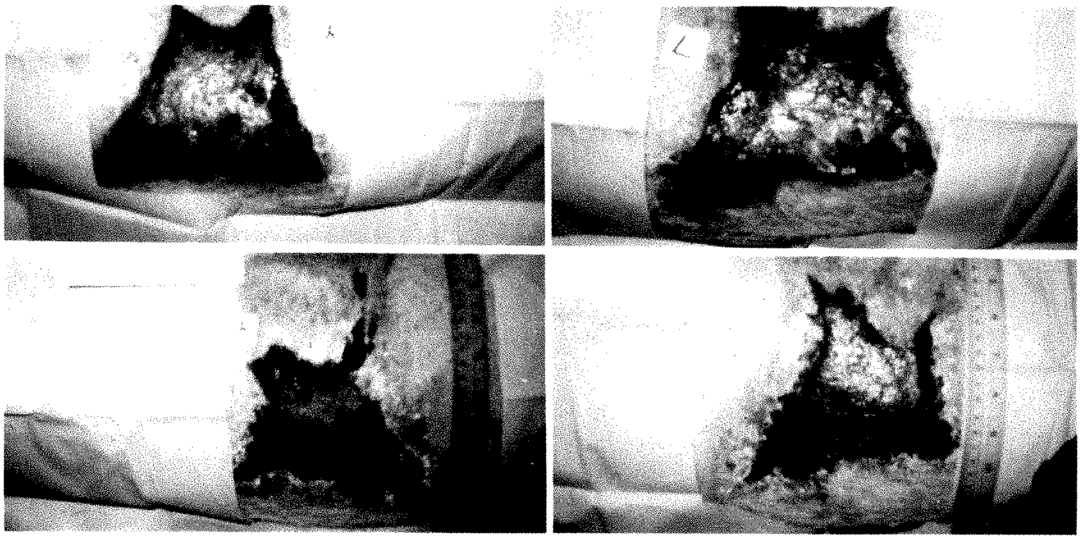
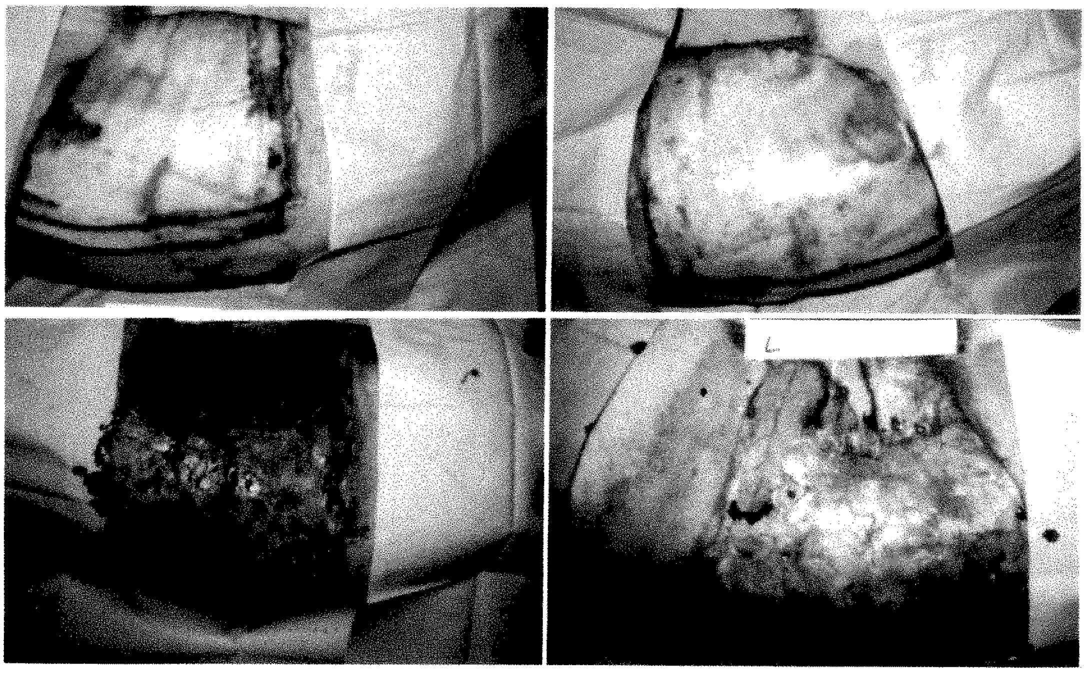


FIG. 14c. Upper left and right, 26 days after Bromelain debridement; lower left and right, 39 days after Bromelain debridement.

be effective in debriding deep burns in a time occasionally as short as 2–3 days, though often a week or more is required, and there are occasional failures.[76] No systemic toxicity attributable to direct action of the preparation[16,22,29,76] have been reported but there is conflicting evidence regarding the effect of Travase on local and systemic burn wound infection.[39,48,76] Pennisi, Capozzi and Friedman stated that in their experience with 68 patients, no cases of septicemia or toxicity could be related drectly to Travase debridement, but no details of those patients developing serious local or systemic infection are given. Bleeding of a significant degree occurred in 3 patients in their series, but again no details are given as to when after burn debridement was begun the bleeding occurred. Partial thickness burns were not injured by the Travase ointment treatment. Pennisi and his associates recommended ". . . that no more than 15% of the total body surface be treated with Travase at any one time. This is to lessen the likelihood of significant bleeding, electrolytic changes and bacterial blood stream invasion." There are two recent reports that the use of Travase may increase substantially the incidence and severity of local burn wound infection and consequent systemic infection. Thus, working with rats, Krizek *et al.*[48] reported at the 1974 meeting of the American Burn Association that



FIGS. 15a–c. Effect of surgical excision on third degree burn of pig. FIG. 15a. Upper left and right; 1 day after injury after 24 hour application of buffered vanishing cream, pH 7.4, immediately before surgical excision; lower left and right, immediately after surgical excision.

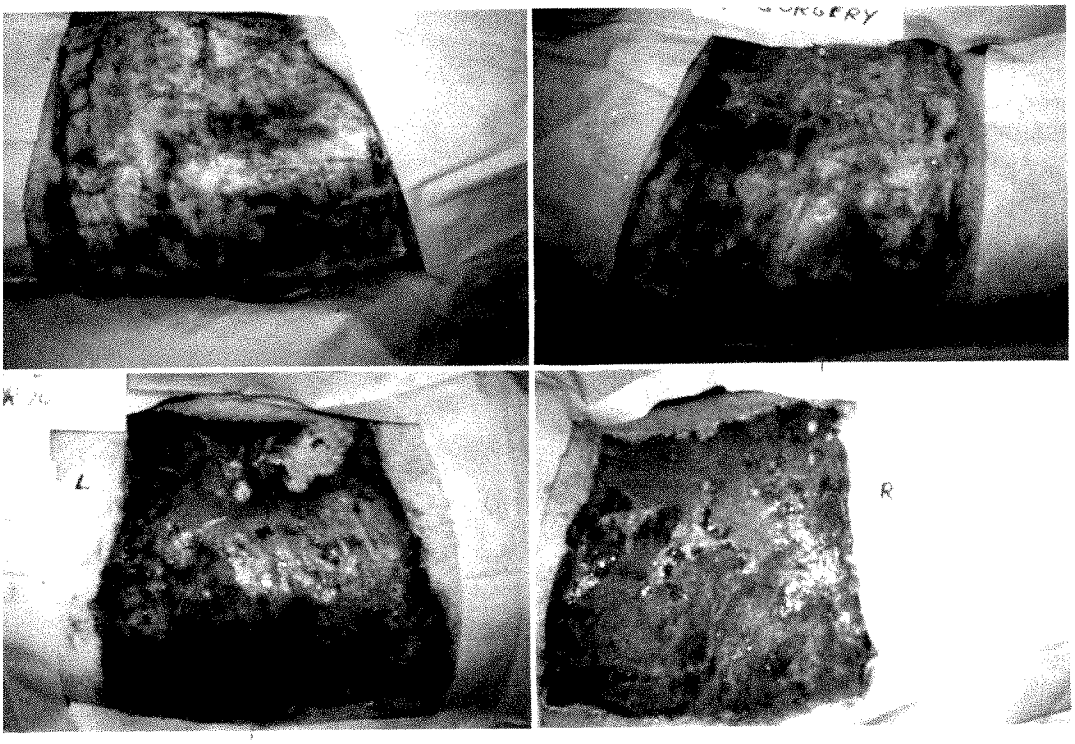


FIG. 15b. Upper left and right, 2 days after surgical excision; lower left and right, 15 days after surgical excision.

> To evaluate the role of sutilains (Travase®) as a contributory cause of burn wound sepsis, the following experimental and controlled clinical studies were performed. Standard 20% full-thickness scald burns were created on the backs of Sprague-Dawley rats. The rats were then divided into various treatment groups and were topically inoculated with 10^8 *Pseudomonas aeruginosa* or left uninfected as a control. Treatment schedules were begun employing sutilains alone, sutilains alternated with mafenide acetate, and sutilains mixed with mafenide acetate. The use of sutilains alone resulted in burn wound sepsis in all rats, even those not initially inoculated with Pseudomonas. Alternate schedules with mafenide acetate did not protect the inoculated animal from sepsis. Neither did the combination of sutilains and mafenide acetate as has been previously reported by others.
>
> Twenty patients with bilaterally symmetrical burn areas were studied. In these patients, one area was treated with moistened sutilains as recommended, alternated with mafenide acetate. The other area was treated with moist dressings, impervious coverings, and alternated with mafenide acetate. Wound progression was measured with quantitative bacterial analyses on tissue biopsies. All patients had markedly increased bacterial counts when impervious wet dressings were used, with or without sutilains. The alternate use of mafenide acetate did not protect the patient and bacterial counts routinely were greater than 10^5 bacteria/gram of tissue.

Hummel *et al.*[39] reported at the same 1974 meeting of the American Burn Association that

> Although the early use of this agent (Travase®) gave prompt debridement of the burn eschar, it resulted in increased fluid loss from the area treated, considerable oozing of blood, and septicemia. The first two patients treated with Travase® enzymatic debriding agent as the initial topical therapy were the only two in which the enzyme was markedly effective in causing rapid separation of eschar. However, both patients developed septicemia from the organism cultured from their burn wound (Proteus and Herellea). Both patients later expired, one from sepsis and the other from exsanguinating hemorrhage.
>
> A series of 11 patients transferred from other institutions were treated with Travase® combined with silver sulfadiazine in the early care of the burn eschar, and showed a much higher incidence of septic complications when compared to burns of similar size, depth and age group treated by other methods such as surgical and laser excision of the burn eschar.

Clearly, there may be a hazard associated with the use of Travase, as employed by Krizek and Robson and Hummel and associates, analagous to the experience of Dimick and Sullivan with Paraenzyme. In our view this hazard may be related to the relative slowness of debridement and the closed dressing technique used. When debridement consists chiefly of fragmentation and solubilization of the burn eschar and several days or more are required for full debridement, the burned area under the closed dressing becomes an excellent culture media for any bacteria present, much more so than the unfragmented burn eschar treated with a local chemotherapeutic agent alone, where spontaneous sloughing is relatively slow, with or without a dressing.

These data indicate to us that a faster acting debriding agent which can be combined with effective local antibiotic or chemotherapeutic agents would be preferable and that it be applied promptly after the burn is sustained. Bromelain may be such an agent.

Bromelain, prepared from the stem of pineapple plants, was used by Klein for the debridement of burns in young pigs and some years ago (the early 1960's) in burned patients. He reported that small 3rd degree contact burns in 3 week old piglets were rapidly debrided in 6 hours and that autogenous skin grafts applied immediately showed a full take after one week.[44] Klein felt that the Bromelain he was using in the early 1960's was effective in patients, but adequate control sites were not followed simultaneously. Also, he found a lack of uniformity of the early Bromelain preparations. More recently, working with better standardized preparations, he reported that when Bromelain was applied as a paste (50% Bromelain, 50% 0.9 saline) to 12-hour-old 3rd degree brand burns of 3 week old piglets under a plastic dressing, within one hour

> . . . the edges of the eschar had lifted and were separated in the entire circumference of the burn from the edge of the adjacent non-burned skin surface by a groove with capillary bleeding exposed. A blunt wooden tongue blade was easily slipped into this groove, and by gentle pressure, not exerting any undue force, readily advanced underneath the eschar along an apparently well demarcated, almost predissected plane between devitalized eschar and viable wound base, in this way easily, with little blood loss, lifting, almost peeling, the eschar off the wound bed . . . leaving a clean wound base of viable tissue ready to take a graft. This experiment has been performed many times on piglets followed by grafting with all grafts having taken. No adverse systemic side-effects have been seen. Controls have been done using Normal Saline only instead of Bromelain, and in our series have not shown the pronounced demarcating effect as described above after Bromelain paste application.[45]

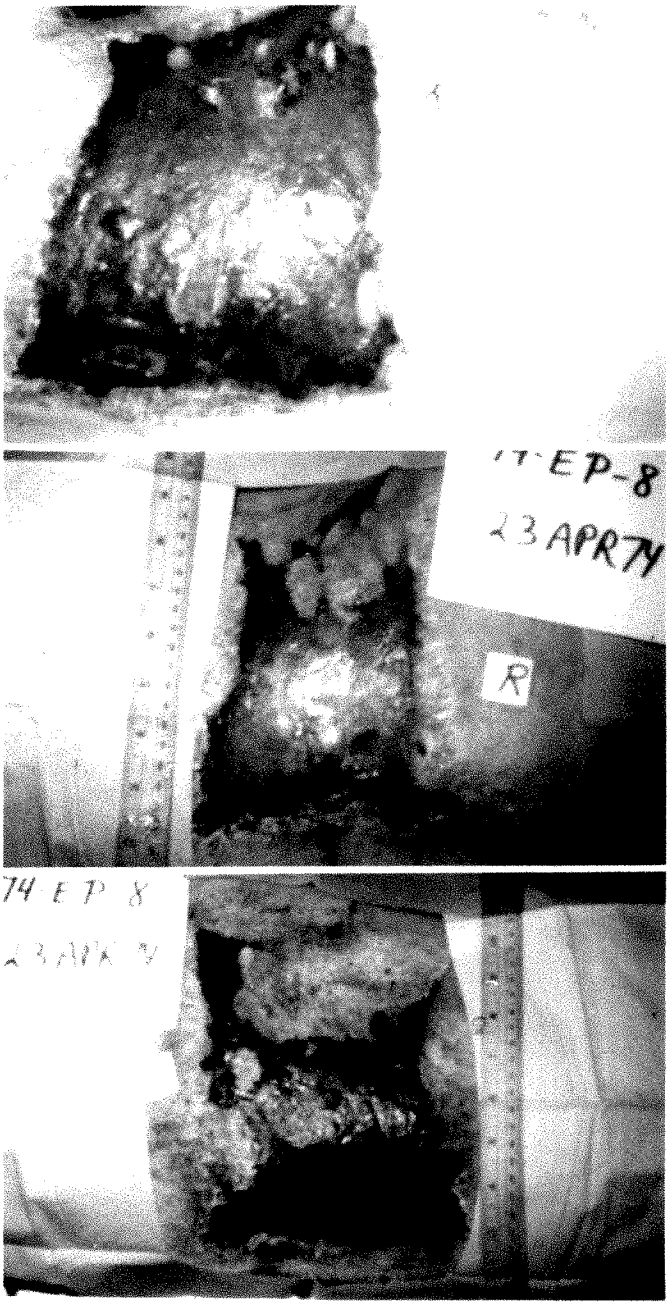


FIG. 15c. (Top) 22 days after surgical excision; (Center and Bottom) 34 days after surgical excision.

He stated that similar results were obtained when the application of Bromelain was delayed until the 5th day after burning.

Klein has also reported verbally that a 50% suspension of Bromelain in 0.9% NaCl solution applied shortly after burning to a small 3rd degree contact burn on the thigh

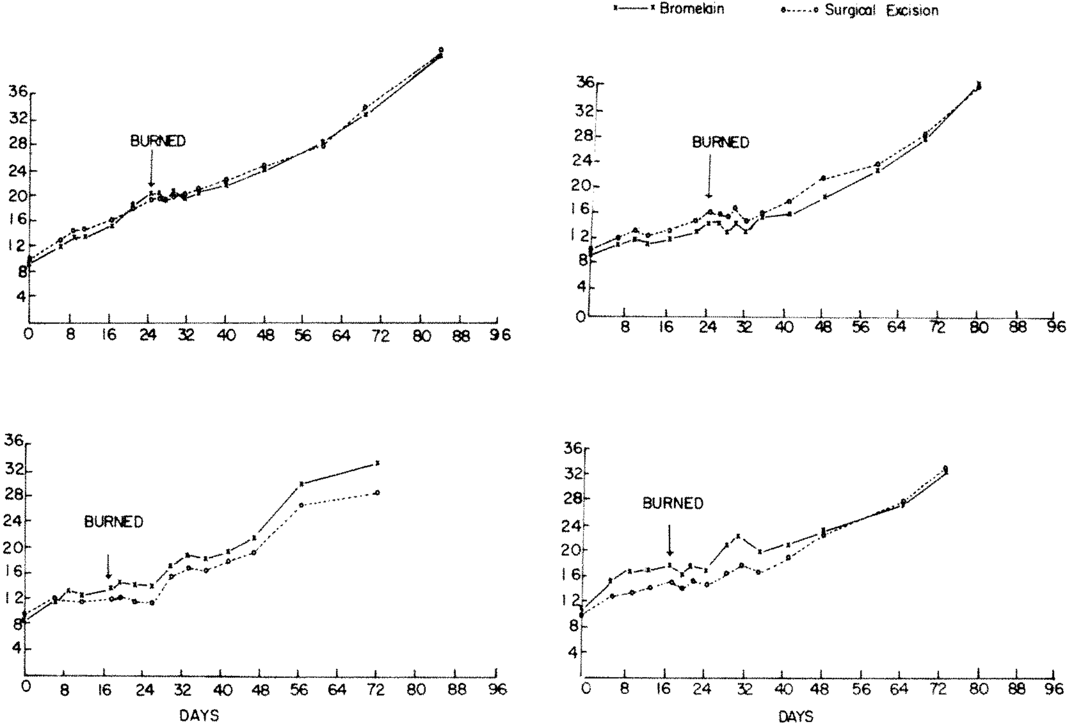


FIG. 16. Effects of Bromelain in buffered vanishing cream, pH 7.4, debridement or surgical excision of large third degree burns of pigs on body weight.

of a human volunteer (himself), resulted in very prompt debridement (a few hours) and that a skin graft applied several hours later to the debrided site took fairly well. He ascribed the failure of the graft to take completely to movement of the graft.[46]

Our earlier investigations reported by Levine *et al.*[54] included *in vitro* tests with full-thickness burned and unburned pig skin with a number of commercial enzyme preparations including hyaluronidase, papain, collagenase (2 different preparations, one of which is currently marketed for human use), a fungal polysaccharidase, a mixture of pancreatic enzymes, Bromelain, H-T Proteolytic (a commercial enzyme mixture which is a baiting agent), ficin, Mylesyme 8-x, and pancreatic lipase. The greatest dissolution of the burned pig skin occurred when Bromelain was used. The ability of Bromelain to debride burned pig skin was roughly equivalent in the pH range 5.5. to 8.5. Bromelain has been shown to be more active proteolytically at temperatures somewhat higher than 37°C, but our experience showed it to be satisfactory for fragmentating and solubilizing burned skin *in vitro* at 37C.

Our next step was to choose an ointment base suitable for allowing maximum debriding action of the Bromelain. A large number of bases was tested. We found that a commercial vanishing cream (Ponds), an oil in water emulsion, was excellent, whereas water in oil emulsions (hydrophilic base U.S.P., Aquaphor, Sulfamylon ointment, Polysorb) were not suitable. The Bromelain-vanishing cream mixture was buffered at pH 7.4 with Triscalcium acetate.

Further *in vitro* testing was carried out to determine which antibiotics and chemotherapeutic agents in current clinical use for the local treatment of burns could be used in combination with Bromelain. Sulfamylon, gentamycin, silver sulfadiazine, and neomycin sulfate were tested at concentrations used clinically. The activity of Bromelain was inhibited by 1% silver sulfadiazine (1971), 1% gentamycin, and penicillin in high concentrations, 250,000 units/cc. but not by 10% Sulfamylon, 1% Neomycin sulfate, or 1% tetracycline. Our recent experiments incorporating Bromelain into the present commercial preparation of silver sulfadiazine (1974) reported in this paper have shown that there is only modest inhibition of Bromelain debriding activity when tested *in vivo* with deeply burned rats and pigs. Silver nitrate was not tested; the free Ag^+ would certainly inhibit the enzymatic activity.

Our earlier *in vivo* tests with contact burns in pigs showed that at 2.5% concentration, the daily application of Bromelain accelerated debridement by a factor of two (23 days to 12 days) as compared with vanishing cream-Tris buffer. The underlying tissue following enzymatic debridement was a clean pink granulating base. No damage to surrounding unburned skin was noted except for some occasional erythema, generally transient.

The species of bacteria found in the pig burns are similar to those found in patients and included *Pseudomonas aeruginosa*, Proteus, Klebsiella, aerobacter, *E. coli*, and Staphylococci. The action of Bromelain was not accompanied by any change in the qualitative and quantitative bacterial counts of the burn surfaces. Nonspecific bacterial debridement as a cause for the accelerated debridement by Bromelain could thus be ruled

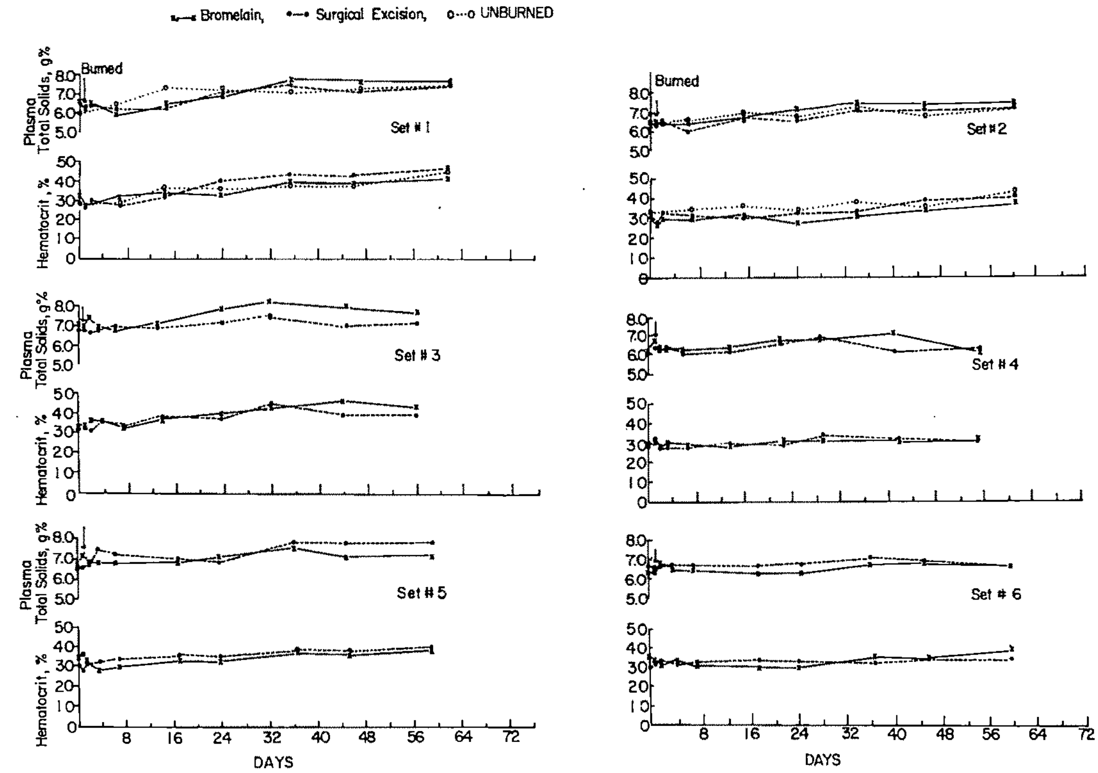


FIG. 17. Effect of Bromelain debridement or surgical excision of large third degree burns of pigs on the hematocrit and plasma total solids of pigs; unburned pigs as additional controls.

out. Sulfamylon (10%) itself slowed spontaneous sloughing (28 days with Sulfamylon vs 23 days for the vanishing cream control). When Bromelain was used with Sulfamylon, the time for complete debridement was reduced to 16 days. There was a modest depression in the number of bacteria in the burns treated with either Sulfamylon or Bromelain plus Sulfamylon when compared to the control (vanishing cream-Tris buffer) or Bromelain treated burns. The data suggested that the difference in debridement time between Sulfamylon and control (statistically significant, $p < 0.02$) may be related to inhibition by Sulfamylon of non-specific bacterial debridement, a suggestion which had been advanced by others to explain the seemingly slower spontaneous sloughing of burn eschars in patients whose burns are treated with Sulfamylon.

There were no differences in bacterial cultures attributable to Bromelain in the presence or absence of Sulfamylon, so the effect of Bromelain in accelerating debridement was independent of any change in the number or types of bacteria.

Although the accelerating effect of Bromelain in a concentration of 2.5% on the debriding of third degree burns was highly significant statistically, the time (12 days) required for debridement was not as rapid as desired. We therefore looked for means by which more rapid eschar separation could be achieved.

Daily subeschar injections of small amounts sterile 2.5% Bromelain with or without 10% Sulfamylon led to debridement of third degree contact burns in pigs in 4–7 days (mean 5.2 days) but the underlying subcutaneous tissue showed substantial hemorrhagic necrosis, a finding similar to that reported by Howes and his associates[38] following the subeschar injection of collagenase. This technique was therefore abandoned.

Using a 50% mixture of Bromelain 1200 in buffered (pH 7.4) vanishing cream or in Tris-buffer (pH 7.4) debridement of third degree contact burns in pigs was accomplished after 8–12 hours of treatment; the Bromelain and dressing had been changed every two hours. In most areas, it appeared that the eschar was solubilized layer by layer from the epithelial surface downward. In some areas, however, the entire eschar appeared to have been dissected free from the underlying tissue, rather than debrided layer by layer. A small amount of hemorrhage was noted at the interface between burned skin and viable tissue. Sulfamylon could be used with the 50% Bromelain preparation without interfering with the debriding activity. Although the underlying base appeared clean and pink, the "take" of autogenous skin grafts applied immediately after debridement was poor. Using third degree burns in much younger pigs we obtained uniform debridement of burn eschars within *two hours* following application of 50% Bromelain in vanishing cream (Fig. 2). The debridement in these animals was principally by "dissection," i.e., the entire eschar could be lifted or wiped off rather than by layer by layer solubilization. With these younger pigs, little or no hemorrhage was observed at the interface of the burn and the viable tissue. Skin autografts applied immediately after debridement in these animals showed a disappointing course, similar to that in the larger pigs. We

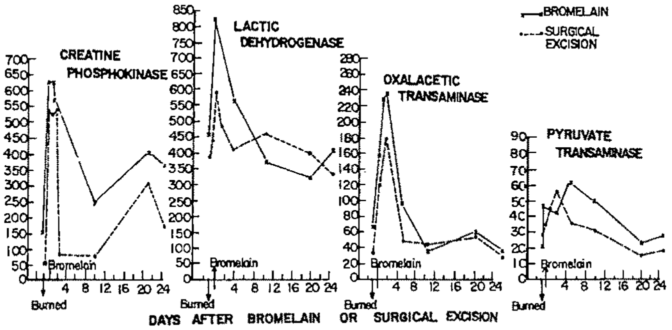


FIG. 18. Effect of Bromelain debridement or surgical excision of large third degree burns of pigs on some plasma enzymes.

believe that the failure of these grafts to "take" is due to the poor vascularity of the pig's subcutaneous tissue rather than to an inhibition of graft take or destruction of suitable graft "bed" by Bromelain, a view supported by our recent studies with rats and dogs; in these species, skin grafts applied promptly after debridement with Bromelain have taken well.

We have found that there is a dose:response relationship when different concentrations of Bromelain in Tris-buffer are used for debridement of third degree burns in rats and pigs. For example, in the case of burned pigs, debridement time varies from hours (25–50% Bromelain) to days (10–20% Bromelain) to weeks (2.5–5% Bromelain). With the high concentrations of Bromelain, the effect on the burned site permitting ready blunt dissection of the eschar was evident before the solubilizing and fragmentation effects were marked, though some solubilization had begun. Thus, it is possible to regulate the rapidity of the Bromelain action in accordance with the goal of the therapy and study.

The specific mechanism underlying the Bromelain effect permitting blunt dissection is not known. It is apparent that Bromelain affects both the burn eschar and the interface between the devitalized burned tissue and the underlying viable tissue. Whether the latter is a reflection of the Bromelain action directly or of an activation or inhibition of certain tissue components, e.g., ezymes, present at the junction between dead and living tissue, or a combination of these factors remains to be determined.

The pig is not an ideal laboratory model for burns in patients since, as mentioned in our results, it is possible to avulse the burn eschar of pigs following hydration of the eschar with a chemically relatively inactive material such as Tris-buffer or vanishing cream. However, much more force is required when Bromelain is used. It should be noted that it is also possible to avulse burn eschars in patients[35] but much more bleeding is seen in patients than in pigs when burn eschars are avulsed forcibly.

In the case of rats with third degree hot water burns, the Bromelain debriding effect was greater in young rats (5–7 weeks of age) than in older rats (3–4 months of age), possibly related to the increasing thickness and keratinization of rat skin with increasing age. For burned rats, the action of Bromelain again consisted of some solubilization of the burn eschar and partial lysis at the interface between burn eschar and underlying viable panniculus carnosus, so that blunt dissection of the residual eschar can be carried out readily. As in the case of pigs, the latter effect appeared somewhat sooner than solubilization of the eschar. Evidence that the underlying tissue was not damaged significantly is apparent from our finding that skin grafts applied immediately after debridement took very well. Similar results were obtained with dogs with contact burns.

If the burn eschar is cross-hatched, the rate of debridement is hastened.

Additional evidence that Bromelain used in the concentrations and times required for debridement induces relatively little local damage is apparent from our observations that such treatment does not modify the rate of healing of partial thickness burns in pigs or injure normal skin. If the skin is nicked during shaving, these areas become erythematous. If 50% Bromelain is applied immediately to areas surgically excised down to muscle, considerable bleeding occurs. Also, if applied to granulating areas, bleeding may occur. These latter observations suggest that the optimum time for the use of Bromelain for debridement of burns is in the early period after injury, before spontaneous sloughing and formation of granulation tissue has begun.

Our studies with rats with third degree burns involving 20% body surface and with pigs with third degree burns involving 15–40% body surface show no evidence of systemic toxicity associated with Bromelain debridement begun 24 hours after thermal injury as judged by general behavior, activity, appearance, weight gain, hematocrit, a variety of blood chemical measurements including plasma total protein, albumin, sugar, urea, sodium, potassium, chloride, calcium phosphate, creatinine, CPK, LDH, SGOT, SGPT, and alkaline phosphatase, formation of granulation tissue, wound contraction, and final healing.

Sterilization of Bromelain can be accomplished without affecting the debriding action by millipore filtration of a Tris-buffer Bromelain solution. This, of course, is an essential requirement for possible clinical use of Bromelain.

Fractionation of Bromelain

We have begun to fractionate commercial Bromelain using various physico-chemical techniques, in an attempt to isolate and characterize the active fractions.

In 1891, Marcano[66] showed for the first time that the juice of the pineapple fruit possesses proteolytic activity.

TABLE 3. *Total Nitrogen; Total Protein and Carbohydrate of Stem Bromelain Eluates*

*DEAE**						*DEAE†*						*G-100‡*							
Eluate Fraction	Vol. ml	T. N. mg/ml	T. N. mg	Biuret mg/ml	Pro-tein g	Eluate Fraction	Vol. ml	T. N. mg/ml	T. N. mg	Biuret mg/ml	Pro-tein g	Eluate Fraction	Vol. ml	T. N. mg/ml	T. N. mg	Biuret mg/ml	Pro-tein g	CHO mg/100 ml	CHO mg
1	300	0.1	36			1	400	0.1	40			1	60	1.0	60	4.1	0.2	80	48
2	120	3.9	468	20.8	2.5	2	100	0.1	10			2	11	1.2	13	5.0	0.1	59	6
3	120	3.8	456	23.3	2.8	3	100	0.3	30			3	11	1.5	16	6.8	0.1	66	7
4	300	1.4	420	8.4	2.5	4	100	0.6	60	3.7	0.4	4	11	1.8	20	9.0	0.1	66	7
5	120	0.3	24			5	100	0.9	90	5.4	0.5	5	11	2.1	23	10.8	0.1	83	9
6	295	0.2	59			6	200	1.2	240	7.8	1.6	6	10	2.6	26	15.2	0.2	50	5
7	245	0.1	24			7	200	2.6	520	16.8	3.4	7	10	3.2	32	19.6	0.2	57	6
8	250	0.1	25			8	100	6.2	620	37.5	3.7	8	10	3.8	38	22.4	0.2	87	9
9	210	0.1	21			9	250	3.4	850	31.0	7.8	9	10	3.8	38	22.6	0.2	133	13
10	150	0.1	15			10	250	0.8	200	8.2	2.0	10	15	2.9	43	16.4	0.2	107	16
	(2110)		(1542)		(7.8)	11	100	0.3	30			11	16	2.0	32	10.8	0.2	133	21
						12	360	0.1	36			12	17	1.8	31	8.8	0.1	133	23
						13	250	0.1	25			13	20	1.8	36	8.0	0.2	93	19
						14	125	0.2	25			14	20	1.7	34	7.6	0.2	20	4
							(2635)		(2776)		(19)	15	70	1.7	119	6.3	0.4	13	9
													(302)		(561)		(2.7)		(202)
Bromelain	50	26.5	1325	200	10		100	26.5	2650	200	20	Bromelain	5	35.8	179	240	1.2		
TRIS												TRIS		1.5		6.1			

* Column (5 × 38 cm.) of 120 Gm. DEAE-cellulose.
† Column (5 × 52 cm.) of 200 Gm. DEAE-cellulose.
‡ Column (2.6 × 91 cm.) of 10 Gm. Sephadex G-100.

TABLE 4. *Enyzmatic Activities* of Stem Bromelain Eluates*
(Casein Digestion Absorbancies at 280 mu and Amylase Activity)

		DEAE					*DEAE*					*G-100*		
Eluate Fraction	T. N. mg./ml.	A(280) 20 ul.	A(280) 100 µg. T. N.	Amylase	Eluate Fraction	T. N. mg./ml.	A(280) 20 ul.	A(280) 100 µg. T. N.	Amylase	Eluate Fraction	T. N. mg./ml.	A(280) 20 ul.	A(280) 100 µg. T. N.	Amylase
1	0.1	0.225	0.162		1	0.1	0.047	0.096	*	1	1.0	0.007	0.175	0
2	3.9	0.835	0.845	*2	2	0.1	0.138	0.158	*	2	1.2	0.198	0.743	*
3	3.8	0.810	0.820	*	3	0.3	0.700	0.800	*	3	1.5	0.560	0.830	*
4	1.4	0.710	0.860	*	4	0.6	0.950	0.835	*	4	1.8	0.788	0.840	*
5	0.2	0.360	0.810		5	0.9	1.08	0.810	**	5	2.1	0.890	0.920	*
6	0.2	0.208	0.715		6	1.2	1.18	0.830	**	6	2.6	0.990	0.830	*
7	0.1	0.328	0.800		7	2.6	1.38	0.885	**	7	3.2	1.06	0.865	**
8	0.1	0.240	0.237		8	6.2	1.36	0.895	**	8	3.8	1.14	0.840	**
9	0.1	0.180	0.240		9	3.4	1.31	0.870	**	9	3.8	1.19	0.885	**
10	0.1	0.160	0.245		10	0.8	0.800	0.840	*	10	2.9	0.995	0.845	**
					11	0.3	0.487	0.900	*	11	2.0	0.378	0.740	*
					12	0.1	0.086	0.960	*	12	1.8	0.033	0.470	*
					13	0.1	0.157	1.5	*	13	1.8	0.020	0.233	*
					14	0.2	0.397	1.5	*	14	1.7	0.004	0.218	*
										15	1.7	0.022	0.184	0
Bromelain		1.30	1.25	***			1.70		***			2.00	0.950	***
Blank			0.105				0.018					0.010	0.133	

* No lipase activity was found in Bromelain or any of the above eluate fractions.
† Amylase activity was graded from 1 (*) to 3 (***).

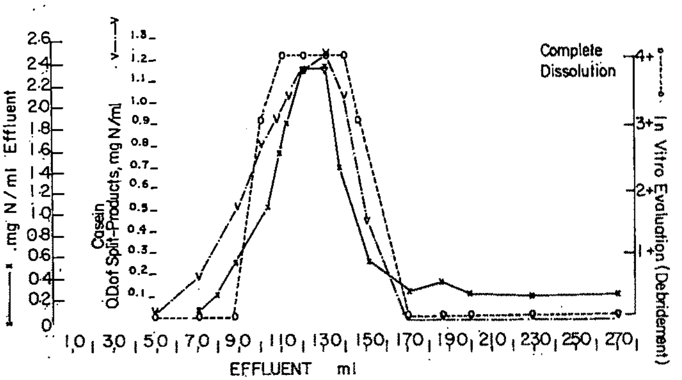


FIG. 19. Fractionation of commercial Bromelain. Sephadex G-100 column, eluted with Tris-buffer, pH 7.4. Note: correlations among N content, enzymatic digestion of casein and *in vitro* debridement of third degree burned rat skin.

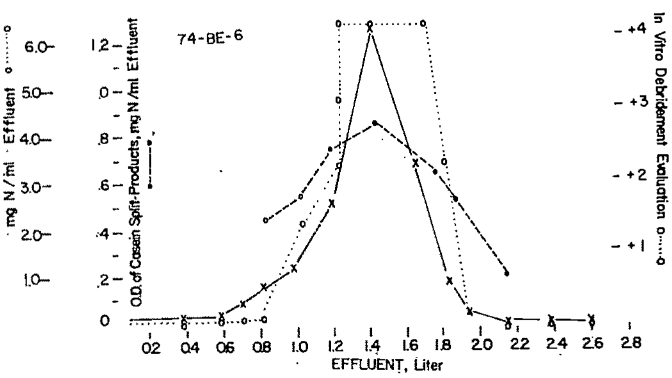


FIG. 21. Fractionation of commercial Bromelain. DEAE-Cellulose column, eluted with 0.02 M and 0.5 M sodium citrate, pH 6. Note correlations among N content, enzymatic digestion of casein and *in vitro* debridement of third degree burned rat skin.

The enzyme in the fruit juice was first described by Chittenden in 1892[10] under the name "bromelin" and is now called fruit bromelain. The occurrence of proteolytic enzymes was also found by Heinicke[33] in the stem juice and such a preparation was named stem bromelain.

The following description of the preparation of stem bromelain is taken from Heinicke[33] and a product description by Dole Company. The raw materials for the commercial extraction of the enzymes are mature pineapple stems. These are collected after the final fruit harvest, cleaned and then pressed to expel the juice which is clarified partially by centrifugation. The centrifuged juice then is subjected to precipitation steps with acetone, the precipitates collected after centrifugation, dried and ground to a dry powder (stem bromelain). Stem bromelain is a mixture of many colloids (including protein, carbohydrates and mucopolysaccharides), inorganic salts and simpler organic materials which are precipitated by acetone. Protein (trichloracetic acid insoluble N × 6.25) generally constitutes about 50% of the total weight of dried precipitate. Inorganic materials, principally cations (calcium, magnesium, potassium, copper and iron) generally make up to 10–15% of the total weight. The balance is assumed to be complex carbohydrate materials of the nature of polyuronides and glycosides. The crude stem bromelain demonstrates considerable proteolytic and acid phosphatase activities and lesser peroxidase, anylase, and pectin esterase activities.

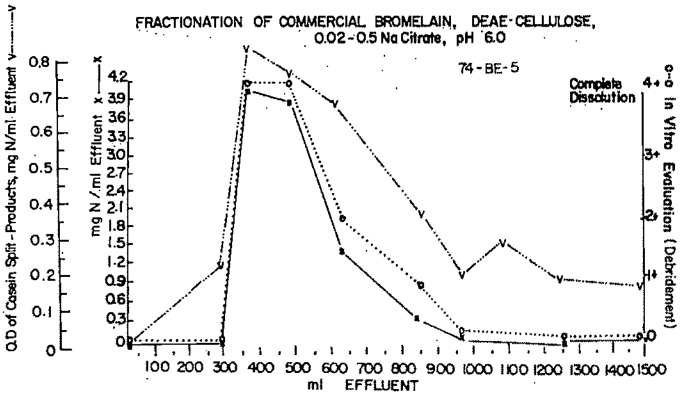


FIG. 20. Fractionation of commercial Bromelain, DEAE-Cellulose column, eluted with 0.02 M and 0.5 M sodium citrate, pH 6. Note correlations among N content, enzymatic digestion of casein and *in vitro* debridement of third degree burned rat skin.

Heinicke and Gortner in 1957[34] were able to separate crude stem bromelain electrophoretically into 5–8 bands; the proteolytic activity was distributed on four bands. From the behavior of the proteases in an electric field, they concluded that the isoelectric points were between 9.2 and 11. Since different pH optima were found for the proteases, they concluded that there was a mixture of four proteases. Using ion exchange chromatography, Murachi *et al.* in 1964[73] were able to demonstrate several chromatographically separable proteolytically active components in such preparations, but found that most of the activity resided in a single component. This was characterized as a basic protein with a molecular weight of 33,000 with one reactive sulfhydryl group per molecule. Its relatively high value of absorbancy at 280 mu suggested a high content of aromatic amino acids. This was later confirmed by the determination of the amino acid composition of this proteolytically active component by both Ota, Moore and Stein[75] and Murachi and associates.[73,74] The presence of only about 2% carbohydrate in the purified enzyme preparation was first thought to represent contamination, but it was subsequently established that this component is a glycoprotein.

Perlstein and Kezdy[77] reported in 1972 that Seven closely related protease inhibitors were isolated from commercial stem bromelain (Pierce Chemical Company) acetone precipitated powder in electrophoretically pure form by gel filtration on Sephadex G-75, followed by

> ion exchange chromatography on DEAE sephadex at pH 7.55. The inhibitors are proteases of MW 5000–6000 which inhibit competively the bromelain catalyzed hydrolysis of CLN (p-nitrophenyl N-benzyloxcarbonyl -L- lysinate) . . . This inhibition is optimal at pH 3 to 4 . . . In the acid pH range, the inhibitors are also effective towards papain, ficin and trypsin.

In our initial experiments, Bromelain, solubilized in Tris-buffer, was then placed on Sephadex G-100 columns and eluted with Tris-buffer, pH 7.4; or DEAE ion exchange columns and eluted with 0.02M and 0.5M sodium citrate, pH 6.0. The eluates were collected in arbitrary fractions. In each case, the proteolytic activity of the various fractions against casein, the ability to attack burn eschar *in vitro* and *in vivo*, and nitrogen content correlated closely. The action against burned skin *in vitro* and *in vivo* was considerably greater than against unburned skin. No lipase activity was demonstrated in any fraction (or the starting commercial Bromelain) but the commercial Bromelain and certain of the eluate fractions showed amylase activity, especially those fractions which demonstrated the highest nitrogen contents and greatest proteolytic activity, indicating that more than one enzyme was likely present in each of the collections showing debriding activity.

Further attempts at more rigorous fractionation of Bromelain are planned by us, with the view of isolating and concentrating that fraction(s) of Bromelain critical for debridement of third degree burns and separating it from all else in Bromelain not necessary for the debriding activity.

We also plan to explore the possibility of synthesizing the active site pentapeptide grouping of Bromelain as determined by Murachi and associates,[74] i.e., Cys-Gly-Ala-Cys-Trp, and determining its possible debriding action.

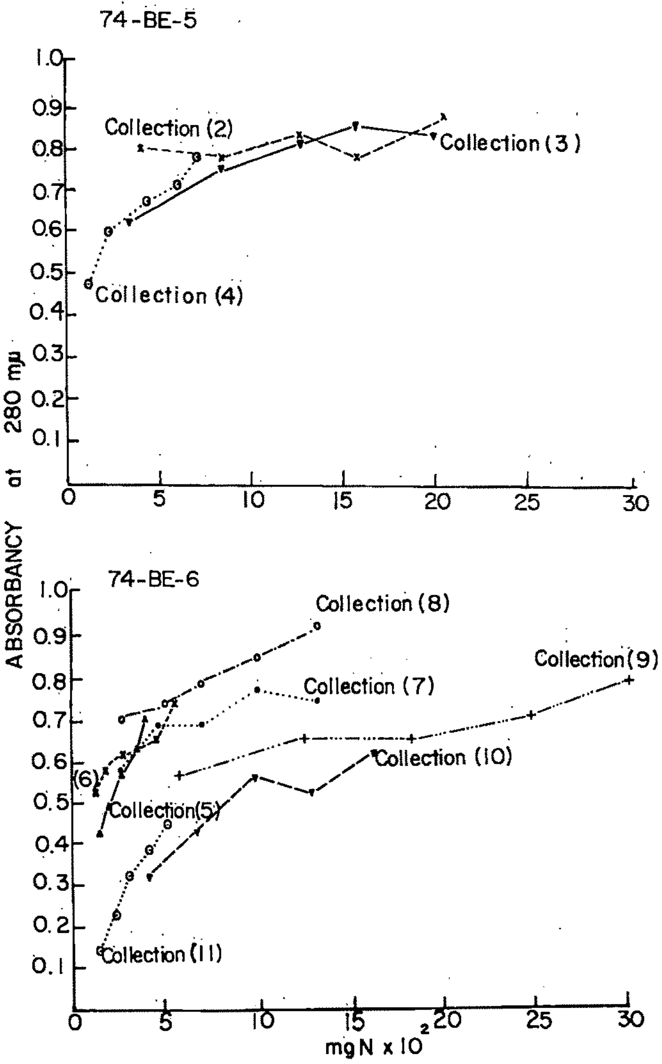


FIG. 22. Rates of casein digestion by various eluate collections of commercial Bromelain; DEAE-Cellulose column, eluted with 0.02 M and 0.5 M sodium citrate pH 6.

Use of Mucolytic and Proteolytic Enzymes for Debridement of Burns

Included in our experimental approach is an attempt to attack the "glue" in the devitalized, burned skin, i.e., the extracellular mucoproteins and glycoproteins and other components of the ground substance, by using hyaluronidase. The thought is that the sequential and possibly the combined use of such enzymes with proteolytic enzymes, such as Bromelain, might lead to increased effectiveness. Thus, it is possible that the hyaluronidase action might remove a "protective" layer of mucopolysaccharides from the collagen fibers and make the denatured collagen more susceptible to protease action. Our initial preliminary *in vitro* experiments with burned skin did not show any special advantage of prior incubation with hyaluronidase, but such an effect has been reported in regard to collagenase activity in the case of normal cornea by Dische, Igals, and Zelmenis[23] and in the case of periodontal ligament by Shulman, Greenspan and Bauer.[86] We plan to pursue this approach further.

Use of Chemicals as Debriding Agents or As Adjuvants for Enzymes Used for Debridement of Deep Burns

There are also non-enzymatic chemical treatments which can mimic the action of the enzymes in decreasing the viscosity of the mucopolysaccharide by breaking either the bonding between the carbohydrates and proteins, by disrupting disulfide bonds in the proteins, or by removal of extracellular ions which stabilize the gross structure of the polysaccharides. Some chemicals may also be used to stress certain links in proteins so that the protein is most susceptible to physical or enzymatic breakdown.

Pyruvic acid was reported by Connor and Harvey,[17]

TABLE 5. *Effect of Various Chemicals on Debriding 3°rd Burned Rat Skin in Vitro**

Chemical	Concentration	Burned Skin	Unburned Skin†
$MnSO_4$	0.250M	1	0
	0.125M	1−	0
	0.075M	0	0
	0.025M	0	0
	0.010M	0	0
N-Acetyl-L-Cysteine	0.010M	3	2−
	0.0075M	2+	1−
	0.005M	2+	0
	0.001M	0	0
	0.0005M	0	0
Cysteine Ethyl Ester HC1	0.100M	3	2+
	0.010M	1	1−
	0.005M	0	0
	0.001M	0	0
Sodium EDTA	1.000%	1	1−
	0.750%	1−	1−
	0.500%	0	0
	0.250%	0	0
	0.100%	0	0
Sodium Salicylate	1.000%	0	0
	0.500%	0	0
	0.100%	0	0
	0.050%	0	0
	0.025%	0	0
	0.010%	0	0
Sulfosalicylic Acid	0.100%	2+	2+
	0.050%	2+	2+
	0.010%	1	1
	0.005%	0	0
	0.001%	0	0
Sodium pyrophosphate	1.000%	1+	0
	0.500%	0	0
	0.100%	0	0
	0.050%	0	0
	0.010%	0	0
H_3PO_4	0.150M	2	2
	0.025M	1+	2
	0.010M	0	0
	0.001M	0	0
	0.0001M	0	0
Sodium Citrate	0.100M	0	0
	0.050M	0	0
	0.010M	0	0
2-Mercaptoethanol	1.000M	2	1−
	0.500M	1	0
	0.100M	1−	0
	0.010M	0	0
Pencilliamide	0.500M	2−	1−
	0.250M	1	0
	0.100M	1−	0
	0.050M	0	0
	0.010M	0	0
Bromelain	2.500%	3	2
Tris Buffer (pH- 7)		0	0

* Incubation time: 20 hours at 37 C.

† Each piece burned or unburned skin weighed about 100 mg.

Sulzberger, Kanof, and Baer[91] and Baliarsing and Krishna[5] to be an effective burn debriding agent but this was not confirmed by Lam and Puppendahl[50] or Gimbel *et al.*[30] among others. Salicylic acid (40%) was used with some success in burned animals by Baliarsing and Krishna[5] and Sauter, Buckwalter and Ziffren.[81] These latter investigators also used the fig latex proteolytic enzyme in pyruvic acid in their animals and clinical studies. The data regarding the latter are chiefly anecdotal.

Crawford and Rozner[18] reported in 1966 on the use in burned patients of a chemical desloughing agent, Aserbine—the cream used was a complex one, containing hexachlorophene, methyl p-hydroxy benzoate, propyl p-hydroxybenzoate, malic ester of propylene glycol, malic acid, salicylic acid, and benzoic acid in a bland base. They felt it to be a safe agent and that it accelerated debridement as compared with control areas (how the control areas were treated is not stated and the number of patients with control areas is not clear). We have not seen further reports of experiences with Aserbine.

Our experiments dealt with the testing *in vitro* of a variety of clinical agents for solubilization and fragmentation activities against burned and unburned rat skin. We chose: 1) mercaptans which may cleave certain linkages (disulfide, ester) in proteins and which also cleave protein-carbohydrate linkages; 2) certain metal ions which cause a weakening of protein fibrillar structure; and 3) compounds which can disaggregate mucopolysacchardes. Cysteine ethyl ester (0.01–0.1m), 2-mercapto-ethanol (0.5–1.0m), N-acetyl-L-cysteine (0.005–0.01M) and penicillamine (0.25–0.5m) demonstrated the desired selective action on burned skin as opposed to unburned skin. We plan to test these compounds singly and in conjunction with Bromelain for debriding activity against burn eschars *in vivo*. We believe the sequential or combined use of non-enzymatic and enzymatic agents holds considerable promise for effective, non-toxic debridement of burns. An important feature of the compounds we have so far found effective *in vitro* is that they do not inactivate Bromelain; -SH compounds, in fact, protect Bromelain against inactivation by oxygen.

Improved Methods of "Delivery" of Enzymes and Other Chemicals

Some experimental findings suggest that the effectiveness of enzymes and other chemicals for debridement can be increased by improving the methods of "delivery" of the agents to the denatured and devitalized tissue. We have already mentioned the observations that burn eschars treated with Bromelain may be readily separated by blunt dissection at a time when solubilization and fragmentation of the eschar has begun but has not yet become marked. This suggests that the applied Bromelain may penetrate the dead skin directly or at the periphery and act at the interface of living and dead tissue. We propose to suspend or solubilize the enzyme preparations in non-toxic vehicles which will hydrate the burn eschar and carry the enzymes into and through the burn slough thereby allowing enzymatic action on the entire thickness of the slough and at the interface of the deeply burned tissue and underlying viable tissue.

Special formulations of vehicles to allow for hydration of the burn eschar, ready penetration of the burned skin by the active enzymes and chemicals, and control of pH will be tried along with various dressing techniques to prevent "drying out" of the applied preparation and burn eschar, since the rate and effectiveness of the chemical and enzymatic debridement are dependent on these factors.

Effect of Debridement and Excision of Burns in Resistance to Infection

We have already described in this discussion the reports of Dimick *et al.*,[23] Krizek and Robson[50] and Hummel and colleagues[42] suggesting that the use of certain proteolytic enzymes preparation for chemical debridement may accentuate remarkably local and systemic sepsis. This, of course, is a very serious matter. It seems to us, as mentioned earlier, that *rapid* chemical debridement, *hours* rather than days, and the combined use of an effective local chemotherapeautic agent with the chemical debriding agent would likely prevent this serious complication. Data have been reported by Levine *et al.*[57] indicating that the very prompt surgical excision of deep burns of rats lessens their susceptibility to purposeful infection with *Pseudomonas aeruginosa* injected i.p. If excision is delayed for 24 hours, the ameliorating effect of surgical excision of the burn is lessened substantially, and may be absent.

In studies to be reported elsewhere, Levenson and associates[52] have been investigating the effects of the early chemical debridement of extensive burns on resistance of the burned rats to infection starting in the burn and infection following an exogenously induced bacteremia. Baseline studies using surgical excision and immediate wound coverage have been carried out so far.

We have found the following in rats with third degree hot water burns over their backs involving 30% body surface and given saline i.p. and orally to prevent shock.

1) The burned rats are much less resistant to *Ps. Aeruginosa* contamination, i.v. and topical, than unburned rats when the contamination are carried out immediately after burning; this has been noted previously by others.

2) When purposeful contamination is carried out immediately after burning, i.v. injection of *Ps. Aeruginosa* is more lethal than direct contamination of the burned wound.

3) The burned rats are most susceptible to the i.v. injection of *Ps. Aeruginosa* immediately after the burn. Surprisingly, 24 hrs. after burn they have regained considerable resistance and are not much more sensitive than unburned control rats.

4) Excision of the burned area immediately after burning and with coverage of the excised area with lyophilized pig skin lessens the mortality to the i.v. injection of *Ps. Aeruginosa* just after the burn is inflicted. Excision and wound coverage at 6° and 24° after burning followed immediately by the i.v. injection of the *Ps. Aeruginosa* had no ameliorating effect, but it will be recalled that we have found that by 24° after burn the resistance of the burned rats to the i.v. injection of *Ps. aeruginosa* is much greater than earlier after burning.

Other experiments, using topical contamination of the burn wound, followed by excisions and wound coverage, are in progress.

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DISCUSSION

DR. BASIL A. PRUITT, JR. (San Antonio): Dr. Levenson has quite properly emphasized the importance of the rapid removal of burn eschar in the control of infection in the burn patient. Even with topical chemotherapy, which controls the bacterial density in the burn wound, individual patients escape from control, and sepsis remains the most frequent cause of death in the extensively burned patient. Consequently there has been a renaissance of techniques, either excision or enzymatic, to hasten eschar separation.

There have been many enzymes evaluated and advocated over the years, and all have been found clinically inadequate because of toxicity, destruction of viable tissue, increased infection, or inabiltiy to graft the resulting wound bed. The enzyme which Dr. Levenson has been studying appears promising, but certain questions must still be answered.

First, was there any toxicity to surrounding unburned tissue, since in some of the pigs there appeared to be a skin rash in the immediately adjacent skin? Although there was no apparent systemic toxicity in the animals in this study, is the enzyme free of toxicity when applied in higher concentrations? Since absorption of material through the burn wound is burn size related, it would seem necessary to evaluate systemic toxicity in animals with larger than small focal burns. Additionally, it would seem important to know if any serum proteolytic activity was identified with a prolonged application. Several years ago we had a quick and somewhat dirty look at a crude preparation of this enzyme, and it appeared to inflict a significant mortality of its own. Is the preparation you are currently using a cleaner preparation, and has this been achieved by the fractionation which you have described?

As Dr. Levenson has pointed out, any clinically useful enzyme should ideally be innocuous to viable tissue and one must ask whether this enzyme injured viable tissue and how that was assessed. Another desirable property of enzymatic debriding agents is the ability to consistently produce a graftable wound bed. Apropos of that, it appeared that the rat wounds could be grafted and the pig wounds could not, and I wonder if Dr. Levenson would care to speculate on the reason for this and on whether man more closely resembles the rat or the pig?

Lastly, with regard to infection which has been recently detailed by the Cincinnati group to be significantly increased with the use of any enzymatic debriding agent on burn patients, have you performed similar experiments in a laboratory preparation with a contaminated wound?

Dr. Klein (Brunswick, Maine): This separation of heat-devitalized tissue from viable organism along a heat-predetermined plane seemed at that time already accelerated by a special grade of the commercially available Dole Bromelain, without injury to viable tissue. However, some inconsistency made it mandatory to isolate from this still heterogenous mixture of different active proteins the specific factor(s) that initiated the phenomenon of acceleration of the separation, of thermally denatured from native tissue, and so also, hopefully, explain the biochemical reaction responsible for it, a knowledge without which reproducibility in an assay were not possible.

I was very grateful to have gotten elegant confirmation from Dr. Levenson. I am delighted now to see, that since I have shared my observations and problems with him, he and his group seem to have arrived at a factor somehow similar to the one Dr. John C. Houck and I have isolated and have been working with, as I mentioned a year ago in the International Meeting for Pharmacological Burn Treatment in Milan.

The data shown here by Dr. Levenson are somehow similar to our data, except that we have observed the acceleration of separation of heat-devitalized from viable tissue, enabling us to lift or peel the eschar off after a one- or two-hour single application of our sterile reproducible, water-soluble fraction on the first postburn day, with the exposed burn wound bed immediately accepting an autograft. There was only negligible blood loss, and no sign of toxic reaction.

(Slide) What you see here is going back to a preparation which was made specifically for us, and which, by no means, was what, unfortunately, got into the hands of Dr. Pruitt, and therefore was very difficult to compare.

(Slide) The burn you see here was made on a four-week-old piglet with radiant heat of 360° for thirty seconds. This is, as you see, after application of our special grade Bromelain in a 50% paste for one hour. The eschar peels off, as you see, and this may answer some of the questions of Dr. Pruitt.

The material had been spread on the burn and the entire skin surrounding the burn, outlined by the black line, and as you see, there has not been any effect on this non-burned skin. In addition, in any animal I have treated, I have always placed a little enzyme paste on my own hand, and I have not so far seen any side effects.

(Slide) This burn wound base was immediately grafted with an autograft, and this graft took, and what you can see is a happy piglet about a month later.

(Slide) The same result was seen on monkeys. This is a rhesus monkey with a burn inflicted in the same way.

(Slide) This is after one hour enzyme contact. You see how the eschar peels off, actually separating from the wound; and then leaving this large wound base, which was then grafted, with the graft having taken.

(Slide) In order to justify the continuation of this study, I had to prove to myself that there indeed was the same reaction on human skin, a question very rightfully posed by Dr. Pruitt, only then did I feel we could continue, and therefore on a human volunteer this burn was inflicted under local anesthesia. Again, it's a 5 × 5 cm burn produced by 360° radiant heat applied for thirty seconds.

A biopsy had been taken prior to application of the special grade Bromelain fraction, in order to prove somehow the depth of the burn. The Bromelain fraction was applied about an hour after the burn, left on an hour, and after removal this is the remaining wound bed. This was then immediately grafted with an autograft.

(Slide) This was the appearance of the autograft four days later, and this is six months later.

I have to add that the graft wasn't handled as it should have been. The volunteer had to travel quite a bit after grafting.

It was clear that we had to evaluate and prove, what, indeed, happened in this wound. So I tried to devise an assay—again, the same kind of a burn wound, and I put a pinhole in the center of the burn wound after the burn wound had been completely covered and sealed off—then I placed a premeasured amount of stained, now, a special fraction of Bromelain in the pinhole, and after one hour it had this appearance. It was possible to peel the eschar from the center of the burn toward the periphery, with the devitalized skin still slightly attached there. The hole in the center was from the burr hole I created.

This assay experiment was already done with the special fraction we had extracted from our special grade Bromelain, with an attempt to concentrate not so much on the digestive, but the dissecting property.

Dr. Stanley M. Levenson (Closing discussion): I appreciate Dr. Pruitt's discussion. I want to assure him and assure all of you that if he is cautious, we're doubly cautious, because, clearly, you don't want to introduce a therapy that is going to do harm.

I think all of us who have worked with burned animals will admit, at least I would, that I don't know of a single experimental animal which I'm satisfied closely mimics man; and the problem is going to be, obviously, to define, hopefully, a clean material. And one of the aims, at least of our group, is that the active fraction, the least proteolytically active in the test tube, seems to be a pentapeptide. Our goal is to synthesize that pentapeptide, and then work with it. And then you are dealing with something known, et cetera.

In regard to some of the specific questions that Dr. Pruitt raised; first, the effect on uninjured skin—if the skin is truly uninjured, the Bromelain has no effect. If you cut the skin; if you nick the skin during shaving, then Bromelain does injure it to some extent.

As far as the size of the burn for systemic toxicity, Dr. Pruitt, the burns were not the small burns, but they were burns that involved about 20% of the body surface. We plan to extend this to animals with 40 percent body surface.

I think, though, that, as I mentioned, the material has got to be tested in a whole variety of animals, and a whole variety of species. For example, there is no reason to think the Fischer rat is going to behave like the Sprague-Dawley, versus the Long, et cetera. There's a lot of toxicology that has to be done.

Now, in regard to the question of the clean preparation, I just mentioned to you our goal; namely, to synthesize a small peptide which is going to be active, because in our data so far the debriding activity parallels the proteolytic activity of the fraction which we have isolated.

As far as the question of grafting, we use fairly large pigs, not piglets, the way Dr. Klein did. Our pigs were around 50–60 pounds. These pigs have a fatty, relatively avascular layer, and, at least in our laboratory, even if we excise uninjured pig skin just below the surface, we have a very poor take of graft. So, in fact, we don't try to graft the pig—the large pig—which has been debrided with Bromelain. We feel the bed is just inappropriate, not because of the Bromelain treatment, but because of the nature of the animal.

A Saga of American Surgery:

The Transactions of the American Surgical Association

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In 1959 it was my privilege to become a member of the American Surgical Association. Realizing that I was poorly informed concerning the origin, evolution, and objectives of this organization, I turned to the Transactions of the Association for enlightenment. Fortunately, the library at our local medical college contained a complete set of these volumes. What began as a Sunday afternoon venture proved so engaging and so informative that it was to continue through the leisure hours of weeks to come and was not concluded until I had enjoyed at least a brief inspection of the contents of every volume which the Association had published during the 81 years of its existence.

My attention was first directed to Volume I, for the years 1881–1883. On the front of this volume there appeared a gold seal bearing the words "Societatis Chirurgica Americana—Instit. A.D. MDCCCLXXX." The negative of this seal, printed in black, appeared on the title page. Volume II was inscribed in the same way. In the third volume, however, for the year 1885, the seal had been altered by the addition of the bust of a man in left profile, in which form it persists at the present time (Fig. 1). On reading further, and after finding an excellent photograph in the front of Volume II (Fig. 2), I realized that the profile was that of Dr. Samuel David Gross, Founder of the Association, who had died three days after the 1884 meeting. Heretofore the name of Dr. Gross had meant very little to me; indeed, I was not even aware that he had organized and founded this Association. To the student of the Transactions, however, his figure emerges quickly in proper proportion, and the force of his personality soon becomes evident. References to his own appearances before the Association and to subsequent historical articles which deal with his contributions to this organization are cited in Table 1. Although Dr. Gross died only three years after the founding of the Association, his influence continued to be evident many years thereafter.*

Perusal of the early volumes disclosed the interesting fact that the leaves of several of them were uncut. Later a notation was encountered stating that when the first volume of the Transactions was printed, covering the years 1881–1883, a copy of the unbound leaves was sent by the Recorder to Dr. Gross for his inspection and approval. Dr. Gross returned the volume with a note of commendation concluding with the injunction, "Don't cut the leaves." It is recorded that the first volume was issued with uncut leaves, as Dr. Gross had suggested, but nothing is mentioned concerning subsequent volumes. I was interested, therefore, to discover that the uncut leaves continued through Volume 10, 1892, coinciding with the term of Dr. J. Ewing Mears as Recorder of the Association. When the second Recorder took office, the custom apparently ceased. It thus appears that Dr. Mears, a close associate and ardent admirer of Dr. Gross, continued to respect the wish of Dr. Gross as long as his term as Recorder permitted him to do so. There is nothing to indicate why Dr. Gross preferred that the leaves remain uncut.†

Through the years there have been many remarkable addresses relating to the origin, development, and purposes of the Association. Seventeen such references were found, of which eleven were delivered as presidential addresses (Table 2). Of this group, the most comprehensive histories of the Association are to be found in the presentation of J. Ewing Mears in 1908 entitled "Reminiscences of the American Surgical Association" and in the presidential address of Fred B. Lund in 1930, entitled "Fifty Years of the American Surgical Association." These articles should be required reading for all students of the Association. The heart of the Transactions is in the presidential addresses.

It is futile to attempt to enumerate the major scientific contributions that have been recorded in the Transactions. They are too numerous to count. Whatever a surgeon's interests may be today, he will find the record of their development in these volumes. The Association originated in the early years of antisepsis and anesthesia, in the year of the first radical mastectomy and the first partial gastrectomy for cancer, two years prior to the first cholecystectomy, and at a time when appendectomy was uncommon and radiology still unknown. The unique life span of the Association coincides with the origin and development of modern surgery. The work of American authors is supplemented by frequent appearances of foreign guests and honorary members, usually men of great professional stature whose names and reputations have endured. Thus one finds in the Transactions an incomparable historical document in which surgical principles

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* A statue of Dr. Gross was erected in Washington, D.C., in 1897 (Fig. 3).

† In my own library there are three copies of Volume I of the Transactions. In each of them many of the pages are still uncut.

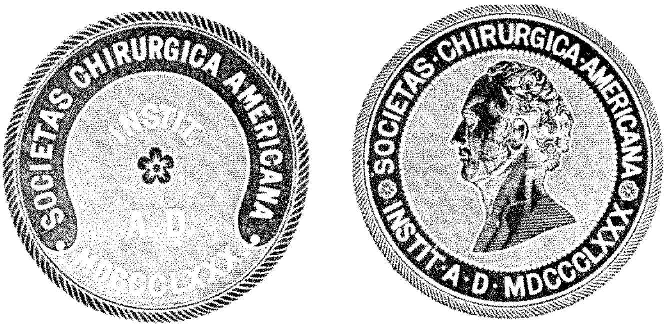


FIG. 1. Seals of the Association.

and practices can be studied from their inception to their present state. The reader will be limited not by the material but only by his own interests and by the amount of time which he desires to spend.

The evolution of contemporary form and style in medical writing can also be observed by the reader of the Transactions. The subdivision into introduction, method, results, discussion, summary and conclusions is a development of recent years. References and illustrations were uncommon in the early years of the Association, and articles were usually long and written in narrative style. Lengthy case lists were frequently appended at the conclusion of the narrative.

Cumulative indices appear in Volumes 10, 20, and 26 (1892, 1902, and 1908). It appears that no index has been compiled since 1908, a period exceeding sixty-five years. Since 1928 most of the scientific publications of the Transactions have also appeared in Annals of Surgery. Those to whom all volumes of the transactions are not available may turn, therefore, to this optional source of reference. Prior to 1928, however, it appears that the presentations were published only in the Transactions.

From time to time comments were encountered in the discussions which are now of especial interest in view of developments which have occurred since the time of their pronouncement. In 1882, for example, there was a heated discussion relative to the merits of antiseptic surgery, including the following remarks of Dr. J. W. S. Gouley of New York: "I do not think that Listerism is going to die—it is dead. Few surgeons will long continue to use it." In 1924, when Drs. Graham, Cole, and Copher presented their method for radiographic demonstration of the gallbladder, it evoked the following remarks from Dr. John B. Deaver: "Referring to Dr. Graham's method, I think possibly in an occasional instance this may suffice, but it strikes me this is another instance of machine power overcoming man power. In my experience gallbladder diagnosis is not difficult; careful palpation and inspection with the proper interpretation of a carefully written history usually suffice to make this diagnosis clear . . . It is a question whether I would not as soon have an operation as to have an injection into my blood system, which must carry more risk than opening the abdomen." These and similar comments should serve to remind the young reader that "the printed page is not the truth nailed down, but rather the author."

The young man undergoing surgical training today may find it difficult to realize that there was ever a time when the American Board of Surgery did not exist; he is unlikely, moreover, to have any idea of the manner in which this Board originated. Candidates for examination by the Board should read the presidential address entitled "Higher Degrees in the Profession of Surgery" which was delivered by Dr. Edward W. Archibald of Montreal in 1935. The suggestions which were made in this address led to the formation of the American Board of Surgery in 1937.

Specialization and sub-specialization are conditions which the young surgeons of this era are likely to take for granted. The evolution of the various surgical specialties can be traced in the Transactions. Dr. S. D. Gross, the Founder, remarked that "It is safe to affirm that there is not a medical man on this continent who devotes himself exclusively to the practice of surgery." It is recorded in the Transactions that Gross, Keen, and others of this period conducted large general practices. Dr. W. T. Bull of New York, who began his practice in 1875 and became a member of this Association in 1882, is said to have been the first American to devote himself to surgery alone from the start of his practice. As recently as 1933 Dr. Arthur Dean Bevan made the following comments regarding specialization to the Associa-

FIG. 2. Samuel D. Gross (Facing title page, Vol. 2, 1884).

TABLE 1. *Relation of Dr. Samuel D. Gross to the American Surgical Association*

Volume	Year	Subject Material
1	1881–3	Address of welcome by the President, Dr. S. D. Gross, delivered at Philadelphia, May 31, 1882.
1	1881–3	Remarks by Dr. Gross on his renomination for President, Philadelphia, May 31, 1882.
1	1881–3	Address of welcome by the President, Dr. Gross, delivered at Cincinnati, May 31, 1883.
1	1881–3	Valedictory address by Dr. Gross on his retirement from the Presidency, Cincinnati, May 31. 1883.
1	1881–3	The first of two scientific presentations by Dr. Gross to the Association, entitled "Value of Early Operations in Morbid Growths"; read June 1, 1883.
2	1884	Second and last scientific presentations of Dr. Gross to the Association, "Wound of the Intestines". Because of the illness of Dr. Gross this was read by Dr. T. G. Richardson of New Orleans.
2	1884	Telegram to Dr. Gross from the Association.
2	1884	Photograph of Dr. Gross
3	1885	Memoir of Dr. S. D. Gross written by Dr. P. S. Connor. The profile of Dr. Gross is added to the Seal of the Association.
12	1894	Presentation and photograph of gavel made from office chair of Dr. Gross; donated by Dr. J. Ewing Mears.
15	1897	Presentation of Gross Statue in Washington, D. C. History of the statue and addresses by Drs. C. H. Mastin, G. M. Sternberg, and W. W. Keen.
26	1908	"Reminiscences of the Early Days of the American Surgical Association", by Dr. J. Ewing Mears, containing historical information concerning Dr. Gross and his relation to the Association.

tion: "What would become of general surgery if the head, spine and peripheral nerves were lopped off by the neuro-surgeons, if the specialists in thoracic surgery took over the chest, if urologists took over the genito-urinary organs, proctologists the rectum and colon, orthopedic surgeons fractures and dislocations and the extremities, and plastic and oral surgeons appropriated their own special field? The gynecologists and obstetricians have for a long time claimed the female genito-urinary tract as exclusively their own. This would leave to general surgery nothing except that small part of the body between the diaphragm and the umbilicus; and now comes another claimant into the field, the tumor specialist or cancer specialist. I have no hesitation in denouncing the last as a very serious blunder. We might just as well develop specialists in inflammation of all parts of the body as to train men as specialists in cancer involving all parts of the body." These comments of Dr. Bevan's will sound quaint to the young man entering the practice of surgery today, for he has become familiar with all the categories described by Dr. Bevan, and with pediatric and cardiovascular surgeons as well.

Apart from the wealth of scientific and historical material to be found in the Transactions, there is much which is notable for its classic literary style or for its philosophical value. Where, for example, may one find a more lucid and sympathetic characterization of the physician than that of Dr. Edward H. Bradford, who remarked that: "The doctor should be broadly human. He must deal with the vagaries of age and the fancies of youth, the sports of boys and the appetites of men. In his profession he tests the aviator and rations the soldier, estimates the endurance of the laborer, cares for the worried mother and relieves the desk-ridden financier. His thought must reach to the ideals of the clergyman and interpret the flesh-promoted dreams of the man of the world. And in this service, neither the precision of science nor the efficiency of business methods will suffice; for above all else, the practitioner must preserve and exercise the kindly indulgence of a considerable friend. In what academy can these lessons be taught?" And who could want a better definition of surgical progress than that expounded in 1908 by Berkeley Moynihan in his second appearance before this Association, when he said: "In surgery, as in all the arts, progress is usually to be measured by the gradual transition from complex and in-

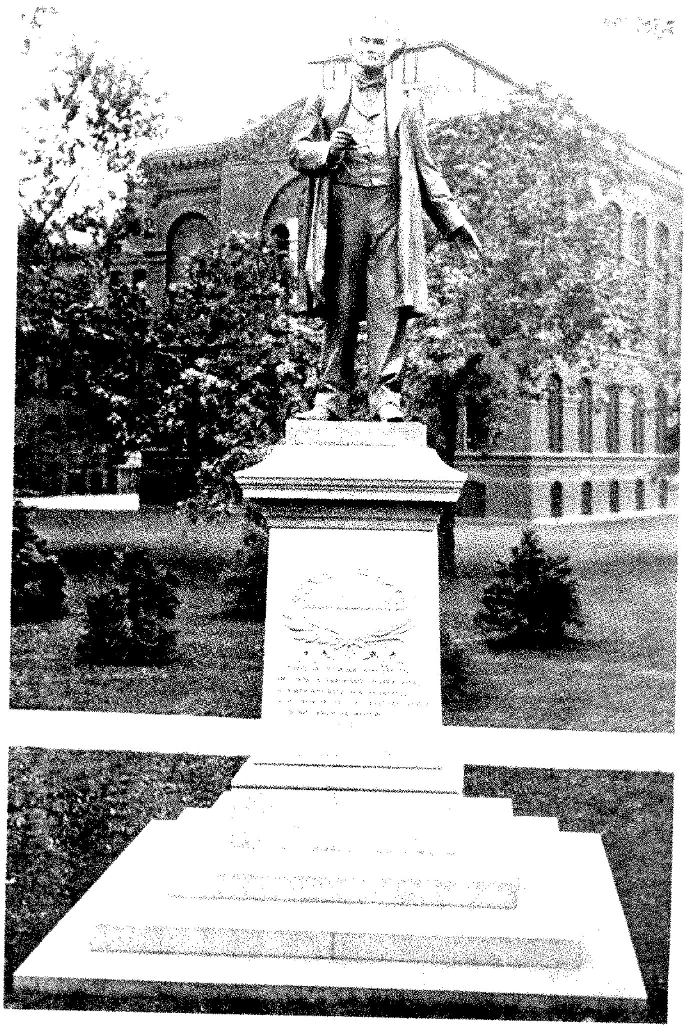


FIG. 3. Statue of Dr. Samuel D. Gross in Washington, D.C. (p. xxx, Vol. 15, 1897).

ABLE 2. *Articles in the Transactions Which Deal with the History, Purposes, Objectives and Development on the American Surgical Association*

olume	Year	Author	Subject Material or Title
1	1881–3	Samuel D. Gross	Remarks regarding origin and purpose of the Association.
3	1885	William T. Briggs Presidential Address	Objectives of the Association and suggestions for their attainment.
5	1887	Hunter McGuire Presidential Address	Suggestions for changes in the Constitution.
9	1891	Claudius H. Mastin	"The Past, the Present, and the Future of Our Association."
12	1894	J. Ewing Mears Presidential Address	"Matters relative to the affairs of the Association."
15	1897	C. H. Mastin, G. M. Sternberg, & W. W. Keen	Addresses on the occasion of presentation of the Gross statue.
20	1902	DeForest Willard Presidential Address	History and future of the Association.
26	1908	J. Ewing Mears	"Reminiscences of the Early Days of the American Surgical Association."
31	1913	Charles A. Powers Presidential Address	"The American Surgical Association. Its Influence on the Growth and Development of American Surgery."
35	1917	J. Ewing Mears	"The Destiny of the American Surgical Association."
48	1930	Fred B. Lund Presidential Address	"Fifty Years of the American Surgical Association."
48	1930	Archives Committee W. L. Estes, Chairman	"Forty Founders of the American Surgical Association" (including their photographs and bibliographies).
51	1933	Arthur Dean Bevan Presidential Address	The Study and Teaching and the Practice of Surgery.
53	1935	Edward W. Archibald Presidential Address	"Higher Degrees in the Profession of Surgery." (This led to development of American Board of Surgery).
55	1937	Evarts A. Graham Presidential Address	"Samuel Gross Looks in on the American Surgical Association."
57	1939	Dallas B. Phemister Presidential Address	"The Development of National Surgical Societies with the Advent of Modern Surgery."
62	1944	Frederick A. Coller Presidential Address	"The State of the Association"
80	1962	J. Englebert Dunphy Presidential Address	Considerations regarding the past and the future of the Association.
86	1968	William P. Longmire, Jr. Presidential Address	"Some Wise Men in American Surgery"
87	1969	Owen H. Wangensteen Presidential Address	"We Cannot Escape History"

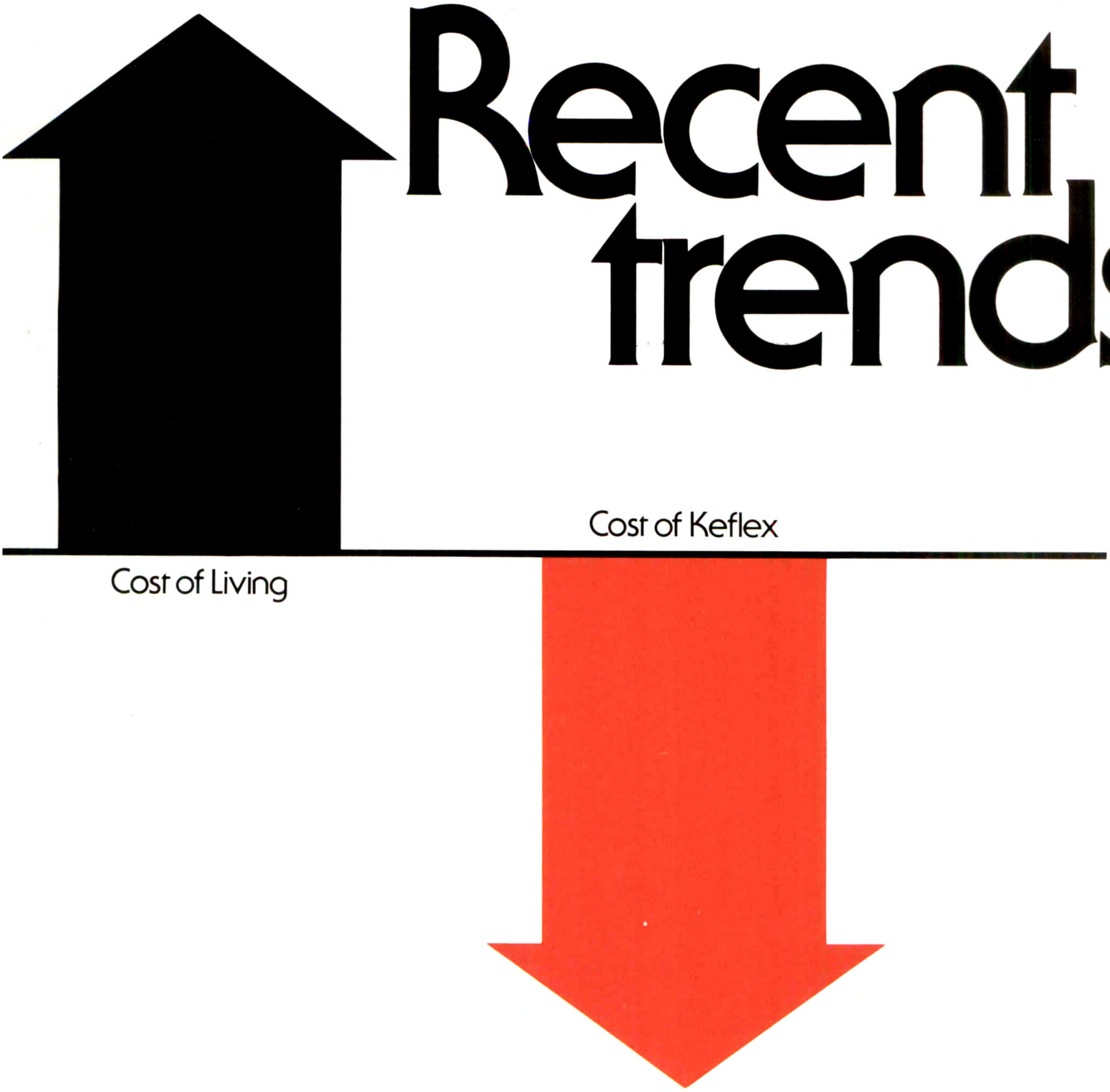
tricate procedures to those of a simpler kind. The tendency in all that refers to the technical apparatus of surgery is always toward simplicity."

Of all my reading in the Transactions, that portion which was to prove most interesting was found in the memoirs of deceased members of the Association. In these biographies men who were known to me by name or by the luster of their works emerged as warm and colorful personalities. One may read, for example, how Hunter McGuire, aware of growing sectional feeling prior to the Civil War, led an exodus of 300 southern medical students from Philadelphia to the Medical College of Virginia in Richmond; how Vilray Blair outfitted a city bus with living quarters and servants for his invalid wife so they could continue to travel together; how John B. Roberts established the Roberts Collection of Portraits of Fellows of the American Surgical Association; how James William White provided in his will a trust to establish a chair of surgical research at the University of Pennsylvania, adding the plaintive stipulation that "in the experimental work necessary for the prosecution of such researches, dogs be used as little as possible, and other of the so-called lower animals be substituted whenever the character of the work permits"; how this same Dr. White fought the last formal duel with pistols recorded in the annals of Philadelphia; how Hugh Cabot explored the Canadian wilderness and sailed the ocean with the Gloucester fishing fleet; how Howard Lilienthal, when his vision failed, wrote stories for children, and how the residents of Barney Brooks served as pall-bearers at his funeral. The soul of the Transactions is in the memoirs.

It was a source of disappointment to me, however, to find that the memoir of my own professor, Dr. Mont Rogers Reid, was missing, along with those of 29 other members who died during the years of World War II. These regrettable omissions were necessitated by restrictions on wartime printing and publication.

Collectively, the Transactions of the American Surgical Association comprise an important historical document in which are recorded the evolution of surgery of the modern era, the development of surgical specialties and of graduate surgical education, and the constantly changing style of medical writing. They may be read with profit by anyone engaged in the practice of surgery or of a surgical specialty. To members of the Association, selected reading of the Transactions is recommended as a means of enhancing their appreciation of the organization and their ability to contribute to its continued scientific progress.

Recent trends



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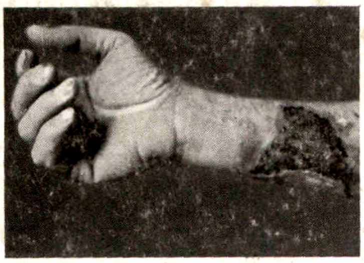

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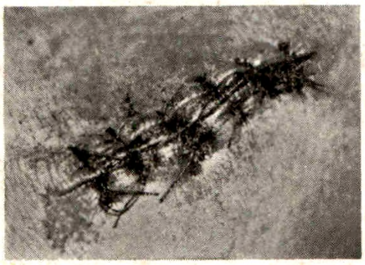

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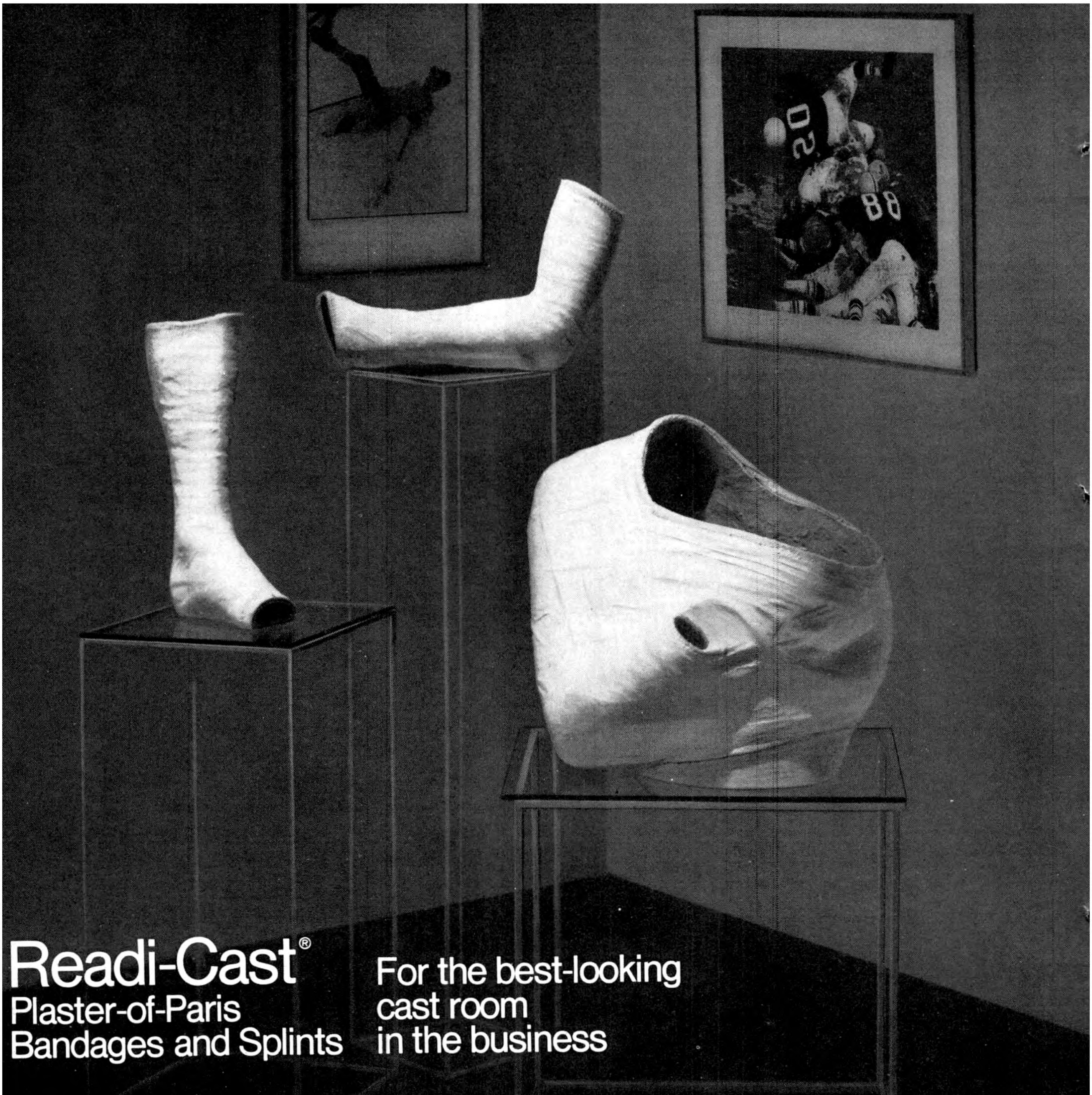

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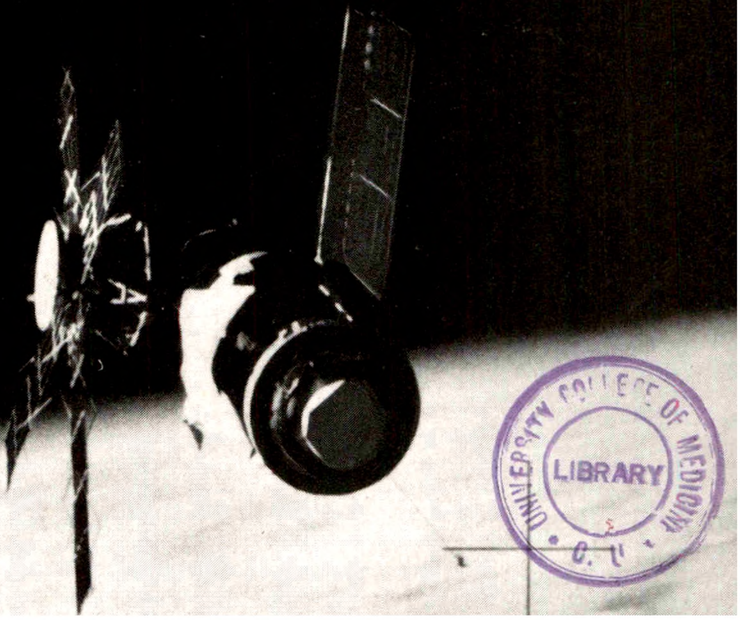

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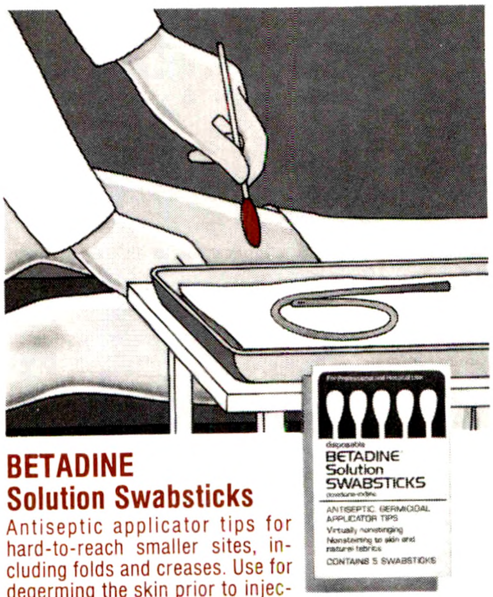
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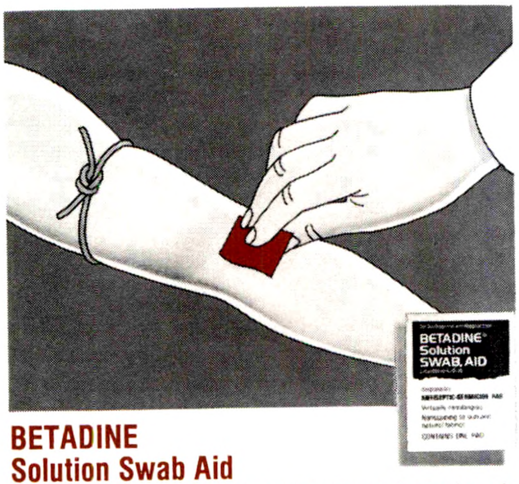

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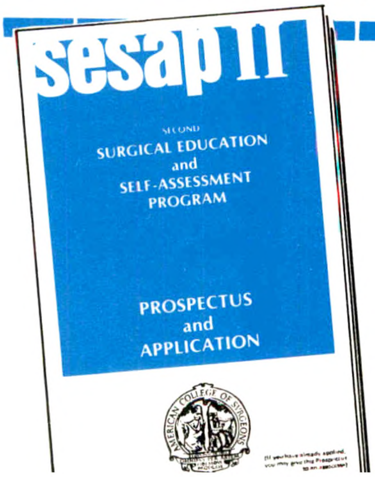

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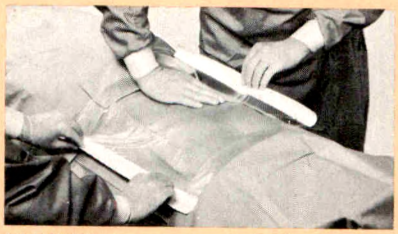

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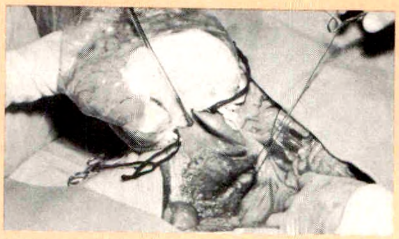

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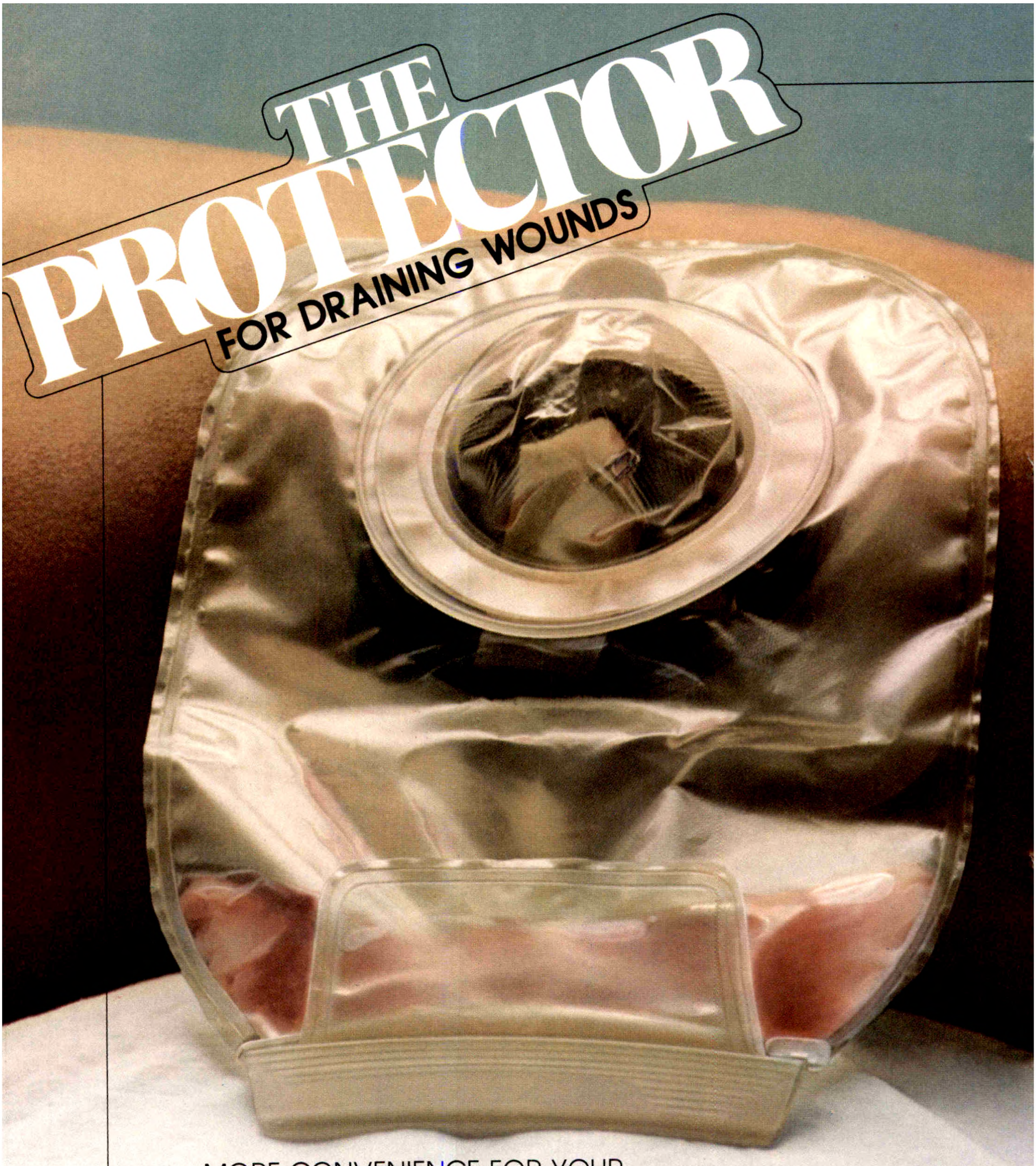

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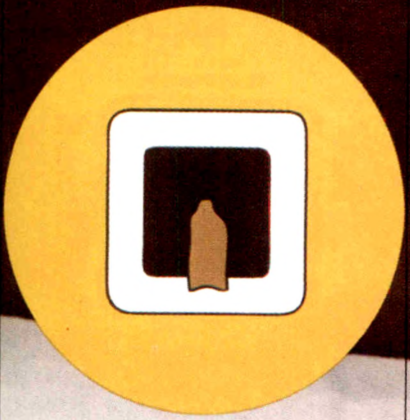

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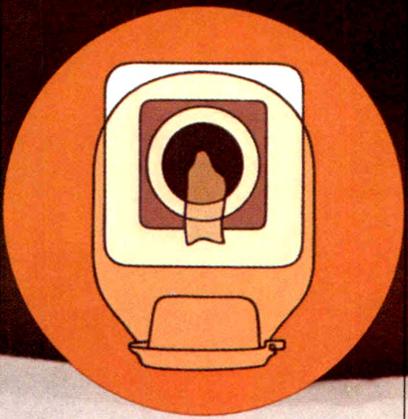

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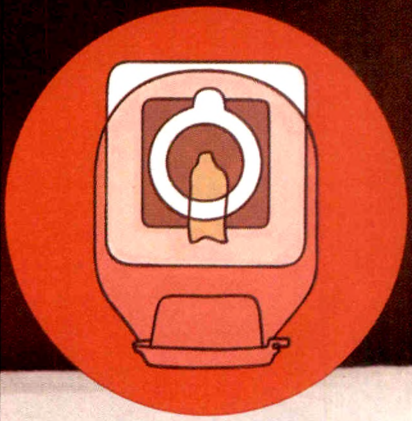

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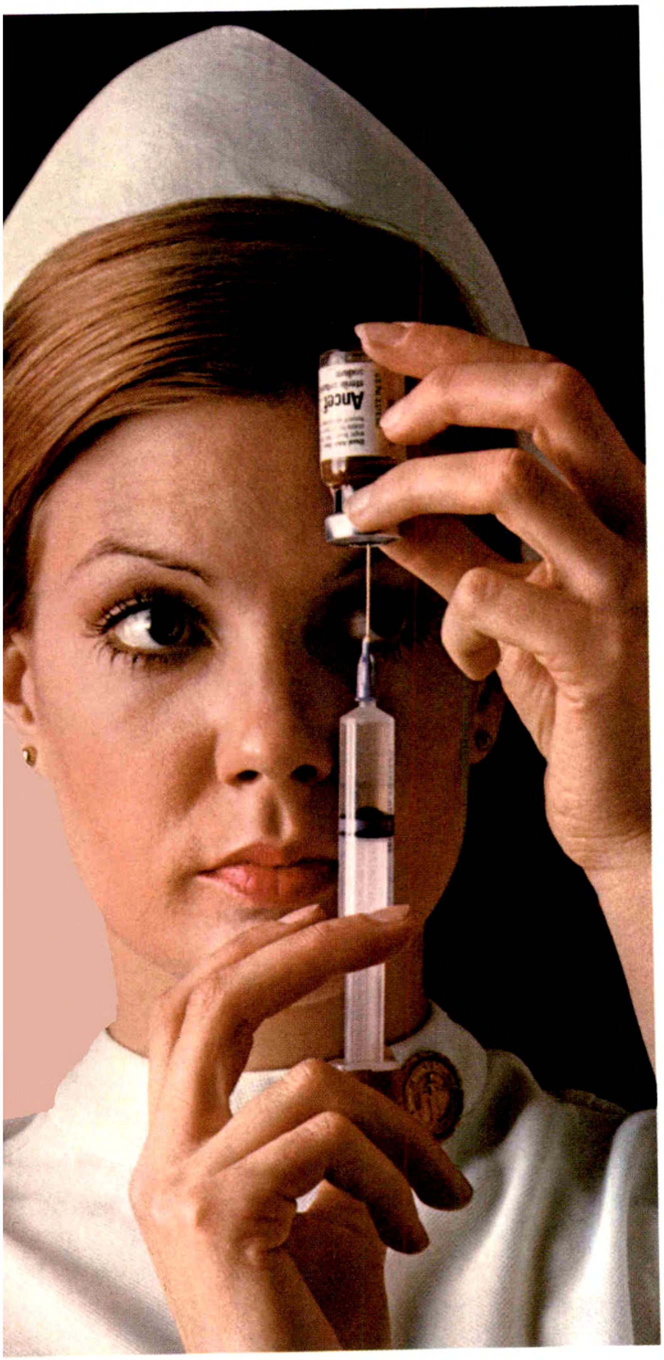

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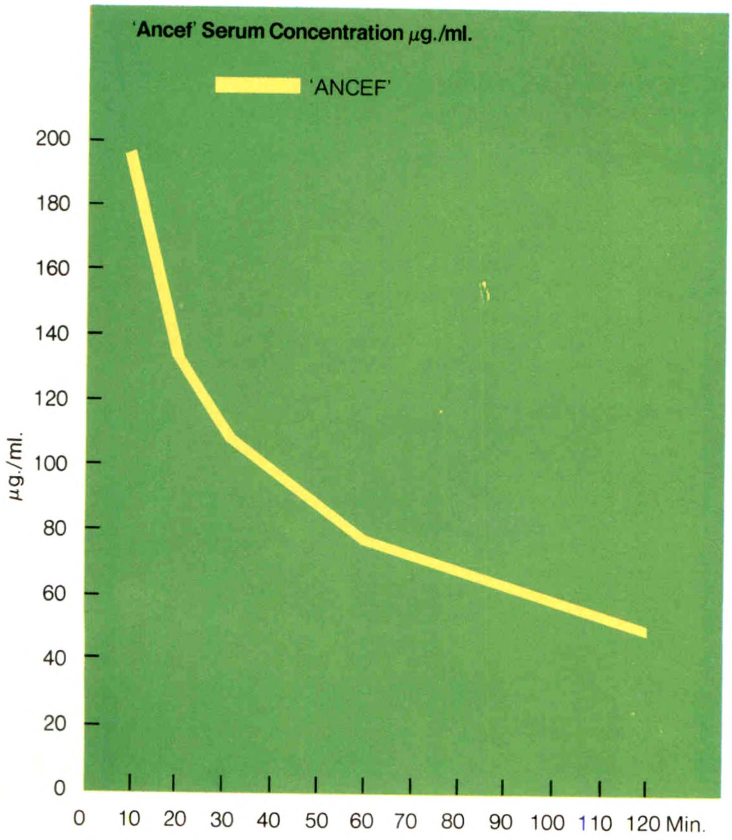

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1 day or less	13	3.0 g.	1
2 days	43	2.6 g.	1
3 days	31	3.3 g.	1
4 days	19	2.6 g.	1
5 days	37	2.6 g.	1
6 days	26	4.7 g.	0
7 days	26	3.8 g.	0
8 days	17	3.0 g.	0
9 days	11	3.1 g.	0
10 days	6	2.7 g.	0
More than 10 days	44	4.9 g.	1
Total	273	3.4 g.	6 (2.2%)

Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. As can be seen in the above chart, which presents the duration of I.V. therapy, average daily dose and the occurrence of phlebitis, most cases of phlebitis occurred in the first few days of therapy which may be indicative that the inflammation was caused by the mechanical trauma of setting up the I.V. rather than continuing irritation of the drug itself.

These data were derived from pre-marketing clinical studies in small populations. Further clinical experience may reveal a greater incidence of adverse effects.

Pain on injection is infrequent with 'Ancef'.

ANCEF® Has Produced No Nephrotoxicity in Extensive Clinical Trials.

(Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.)

Adverse Reactions.

Adverse reactions reported in the clinical trials included: pain on injection, rash, G.I. symptoms, pruritus and phlebitis. For a complete list of adverse reactions associated with 'Ancef' therapy, please see brief summary of prescribing information on next page.

See following page for a brief summary of prescribing information including contraindications, warnings, precautions and dosage.

Smith Kline & French Laboratories
Division of SmithKline Corp., Phila., Pa. 19101

From SK&F...

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

(lyophilized)

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae	*Klebsiella* species
Escherichia coli	*Enterobacter aerogenes*
Proteus mirabilis	*Hemophilus influenzae*

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Diplococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'ANCEF' IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for mild gram-positive infections is 250 mg. to 500 mg. of 'Ancef' every 8 hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every 8 hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 gram of 'Ancef' every 6 to 8 hours. 'Ancef' has been administered in dosages of six grams per day in serious infections such as endocarditis. 'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.) 60% of the normal daily dose given in divided doses q12h should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.) 25% of the normal daily dose given in divided doses q12h should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.) 10% of the normal daily dose given q24h should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dose may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories, Division of SmithKline Corp.,
Philadelphia, Pa. 19101

You don't have to remove the smile when you remove the dressing.

Dry gauze dressings that stick to the wound can hurt. Can damage new tissue.

New, nonadhering AQUAFLO gauze dressings lift off with greatest comfort. Won't disturb healing.

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Postoperative Oral and Intravenous Nutrition

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Oral and intravenous high calorie-amino acid nutritional therapy postoperatively resulted in significant weight gain, improved colonic wound healing and maintenance of normal intravascular albumin levels. Provision of caloric needs without amino acids minimized weight loss postoperatively. However, infusion of hypertonic dextrose solutions resulted in severe generalized hepatic fatty infiltration and marked hypoalbuminemia. Protein and calorie deprivation by administration of 5% dextrose and water resulted in the greatest postoperative weight loss, reduced intravascular albumin levels and decreased colonic anastomotic strength. Comparison of oral and intravenous diet administration demonstrated that hypertonic dextrose infusion was markedly deleterious to hepatic morphology and serum protein metabolism in normal rats. Further clinical investigation appears indicated in previously well-nourished patients undergoing extensive surgery who will not be able to ingest adequate nutrients in the postoperative period.

THE ADVANTAGES of supplying adequate nutrition either enterally or parenterally to the malnourished surgical patient have been well established.[5,6,9,20] Controlled laboratory experiments using malnourished animals have further documented the beneficial effects of providing high calorie-protein nutrition intravenously and orally.[7,10,18] The metabolic benefits of adequate protein-calorie nutritional therapy postoperatively to previously well-nourished individuals have been suggested,[12] but have not been fully investigated. This experiment was designed to assess the effects of postoperative intravenous high calorie-amino acid nutrition, high calorie dextrose infusion, and low calorie (5% dextrose) parenteral solutions on colonic wound healing, serum protein metabolism and body weight change in normal healthy rats. Another objective of this experiment was to observe any differences in these parameters when nutrition was provided orally or intravenously.

Materials and Methods

Sixty adult Sprague-Dawley female rats, weighing 180–210 gm, underwent a standard colonic anastomosis.[3] To insure uniformity, the colon in all rats was transected 1.25 cm above the uterine fundus. Postoperatively, the animals were divided randomly into six equal groups. Three groups were subjected to jugular vein cannulation and thereafter were continuously infused with 30% dextrose-5% amino acids (Group I), 30% dextrose (Group II), or 5% dextrose (Group III) solutions using a specially-designed swivel delivery apparatus which allowed unrestrained activity.[19] These groups received an average of 39–48 ml of fluid per day (Table 1). Three control groups were fed identical solutions orally *ad libitum.* All solutions contained identical concentrations of required vitamins and minerals. At seven days, body weights, bursting strengths of the anastomoses and of adjacent colonic segments, plasma volumes, hematocrit values and total serum protein and protein electrophoresis determi-

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TABLE 1. *Nutrient Groups and Fluid Intake*

	Group I 30% Dextrose + 5% Amino Acids		Group II 30% Dextrose		Group III 5% Dextrose	
	I. V.	Oral	I. V.	Oral	I. V.	Oral
Daily Fluid Intake (ml)	48 ± 10	38 ± 16	39 ± 11	29 ± 14	44 ± 11	111 ± 42
Daily Amino Acid Intake (gm)	2.4	1.9	0	0	0	0

nations were done. Liver sections were studied histologically by H & E and oil red O fat stains to evaluate hepatocellular morphology.

Bursting strengths of anastomotic segments (segment 1) and of adjacent proximal colonic segments (segment 2) were determined by measuring the intraluminal pressure at which the colonic segments burst. Plasma volumes were measured using radioiodinated human serum albumin-saline solution containing 0.1 microcurie ^{131}I. Total circulating serum albumin was computed from serum albumin concentration and plasma volume determinations.

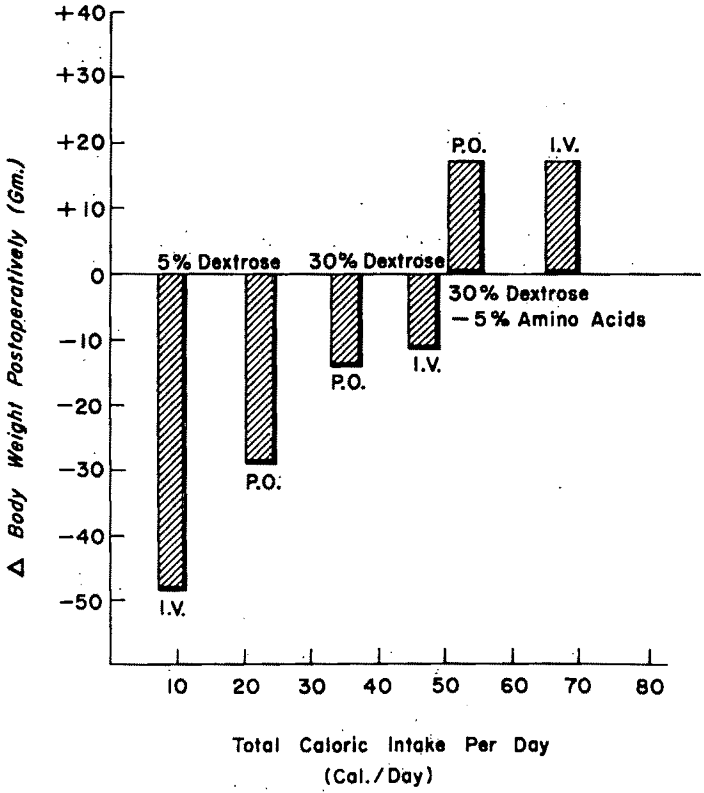

FIG. 1. Postoperative high calorie-amino acid nutrition, intravenously and orally, resulted in identical weight gains significantly different from the other study groups. Administration of 30% dextrose minimized weight loss, but did not allow weight gain. Only by provision of caloric needs plus amino acids was body weight increased postoperatively. Infusion with 5% dextrose and water supplied minimal calories and resulted in the greatest postoperative weight loss.

Results

At seven days, both the intravenous and oral 30% dextrose-5% amino acid groups had identical weight gains which were significantly greater than the other four groups ($p < 0.001$) (Fig. 1). The intravenous group received an average of 335 Cal/kg/day, which was significantly more than the 265 Cal/kg/day ingested by the oral group ($p < 0.05$) (Table 2). Administration of 30% dextrose intravenously and orally resulted in similar minimal weight loss. The intravenous group received an average of 235 Cal/kg/day, while the oral group ingested only 175 Cal/kg/day ($p < 0.05$). The animals given 5% dextrose solutions had the greatest postoperative weight loss. The intravenous group received the lowest daily caloric ration (45 Cal/kg/day), whereas the oral 5% dextrose group ingested an average of 110 Cal/kg/day. The rats fed orally with 5% dextrose solution drank an average of 111 ml of fluid per day, which was a significantly greater volume than the other two oral groups. Mean serum albumin fractions were similar in both the oral and intravenous Group I animals and were significantly greater ($p < 0.001$) than the other four groups (Table 3). Mean serum albumin levels were not significantly different between intravenous animals and their oral counterparts except in Group II. Animals in this group which were infused with 30% dextrose had significantly lower ($p < 0.001$) mean serum albumin values than those drinking the same solution despite the fact that the intravenous rats received significantly more calories per day than their oral controls. Serum globulin values, ranging from 2.6–3.0 gm % were not significantly different among the six groups of animals.

Total circulating serum albumin, computed from the serum albumin concentration and the plasma volume, averaged 0.24 gm in both the oral and intravenous 30% dextrose-5% amino acid groups. Total intravascular albumin in these animals was significantly greater ($p < 0.01$) than in the other four groups. No significant differences in total circulating serum albumin were noted when intravenous animals were compared with oral controls receiving the same diet.

The bursting pressures of segment 1, containing the anastomosis at the center, were highest in the intravenous and oral Group I animals. Mean anastomotic bursting

TABLE 2. *Correlation of Postoperative Body Weight Change With Total Calorie Intake*

	Group I 30% Dextrose & 5% Amino Acids I. V.	 Oral	Group II 30% Dextrose I. V.	 Oral	Group III 5% Dextrose I. V.	 Oral
Number of Animals	10	10	10	10	10	10
Δ Weight (gm)	+17	+17	−11	−13	−48	−29
Total Caloric Intake (cal/day)	67 ± 14	53 ± 19	47 ± 12	35 ± 15	9 ± 1	22 ± 8

strength in the intravenous animals in this group was significantly greater ($p < 0.005$) than in Group II, but not significantly greater than in Group III. Average anastomotic bursting strength in the oral Group I animals was significantly greater ($p < 0.001$) than the other two oral groups. No significant differences were noted in any of the groups when intravenous animals were compared with oral controls receiving the same diet. The mean bursting pressures of segment 2, a proximal adjacent segment of colon, ranged from 182 to 218 mm Hg in the six groups of animals. Because of the large standard deviations, no significant differences were noted among these measurements.

As shown in Figs. 2 and 3, histological examination of liver sections from Groups I and III revealed minimal, predominantly periportal, fatty infiltration. In contrast, liver sections (Fig. 4) from the oral Group II animals showed an increased amount of fatty infiltration. Marked generalized fatty infiltration and vacuolization with distortion of normal hepatic morphology was demonstrated in the intravenous Group II animals (Fig. 5).

Discussion

Although weight gain is now frequently observed in postoperative surgical patients receiving intravenous hyperalimentation, it has been difficult to measure other metabolic and nutritional benefits of high calorie-amino acid parenteral feeding in critically ill patients under controlled conditions. Despite the fact that animal data may not be applicable directly to man, studies in rats allow a degree of control which is impractical to achieve in human beings. Previous experiments in severely protein depleted rats have shown that high calorie-amino acid parenteral feeding allows significant weight gain, serum albumin regeneration, increased colonic anastomotic strength, and restitution of hepatic cellular morphology to normal.[18] The purpose of this experiment was to study the effects of postoperative intravenous and oral 30% dextrose-5% amino acids, 30% dextrose and 5% dextrose solutions on colonic wound healing, serum protein metabolism, and body weight change in normal healthy rats.

Body Weight Change

Postoperative high calorie-amino acid nutrition, intravenously and orally, resulted in identical weight gains that were significantly greater than in all other study groups. In achieving this weight gain, the oral group ingested significantly less isocaloric, isonitrogenous fluid than was supplied to the intravenous group. Oral and intravenous administration of 30% dextrose without amino acids minimized weight loss. However, while the intravenous 30% dextrose group received an average of 47 calories per day and *lost* only 11 gm postoperatively, the oral 30% dextrose-5% amino acid group ingested an average of 53 total calories per day and *gained* 17 gm postoperatively. These weight changes reflect the importance of supplying not only caloric needs, but also amino acid requirements in the postoperative period. Previous studies in protein depleted rats nourished with 30% dextrose demonstrated the development of gross edema after a seven day infusion period.[18] Neither the group given oral nor intravenous 30% dextrose, however, appeared edematous in this experiment. The oral 5% dextrose group ingested the largest fluid volume per day, possibly in an

TABLE 3. *Correlation of Serum Proteins With Colonic Bursting Strength*

	Group I 30% Dextrose & 5% Amino Acids I. V.	 Oral	Group II 30% Dextrose I. V.	 Oral	Group III 5% Dextrose I. V.	 Oral
Serum Albumin (gm %)	3.1 ± 0.4	3.2 ± 0.2	1.9 ± 0.2	2.6 ± 0.2	2.6 ± 0.3	2.5 ± 0.3
Albumin (gm)	0.24 ± .05	0.24 ± .02	0.13 ± .03	0.17 ± .04	0.17 ± .04	0.18 ± .04
Bursting Strength #1 (mm Hg)	188 ± 18	195 ± 8	161 ± 10	159 ± 25	176 ± 10	161 ± 13
Bursting Strength #2 (mm Hg)	218 ± 36	199 ± 19	216 ± 8	200 ± 22	185 ± 25	182 ± 25

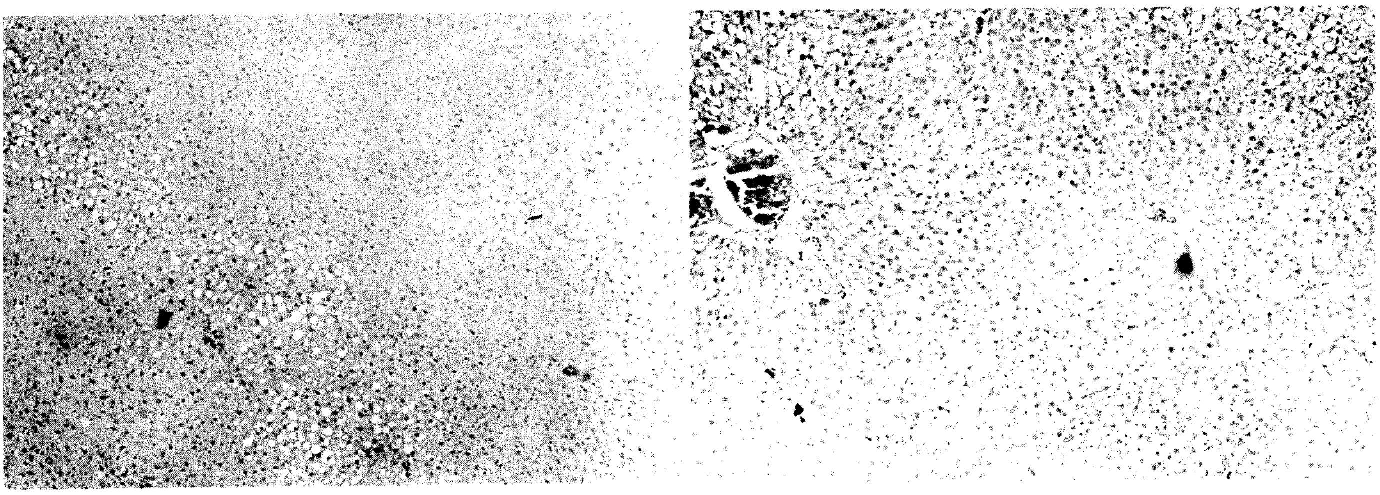

FIG. 2. Mild periportal fatty infiltration in livers of animals given 30% dextrose-5% amino acid solutions intravenously (left) and orally (right). Subsequent studies have demonstrated that fatty infiltration is not a regular occurrence with the administration of 30% dextrose-5% amino acid solutions orally and intravenously. The photomicrograph on the right was taken at a slightly higher power than the one on the left.

effort to obtain more calories. As shown in Fig. 1, the group infused with 5% dextrose (common clinical therapy) received the fewest average calories per day, resulting in the greatest mean weight loss (24%) postoperatively.

Serum Proteins

It is well established that serum albumin levels reflect more rapidly than the total serum globulins any change in the nutritional status of a patient or experimental animal.[11] When animals are deprived of food or placed on a protein-deficient diet, albumin synthesis decreases by approximately 50% within 24 hours, and this low level of production persists as long as the deficiency state is maintained.[16] Fleck and Munro have demonstrated a decreased catabolic rate of serum albumin in rats receiving a protein-deficient diet suggesting an increased half-life of serum albumin as a result of diet.[8]

In this experiment, the animals receiving adequate nutrition (30% dextrose-5% amino acids) maintained normal serum albumin levels postoperatively. In marked contrast, the animals infused with 30% dextrose had a significant decrease in serum albumin and total intravascular albumin levels. The marked hypoalbuminemia noted in this group was unexpected because preoperatively these animals were in good nutritional status. In a previous experiment from this laboratory, the infusion of a high calorie nitrogen-free solution into animals that had been protein depleted for six weeks, produced a kwashiorker-like state with hypoalbuminemia, edema, lassitude and severe hepatic fatty infiltration.[18] Protein depletion in these animals, however, had already lowered serum

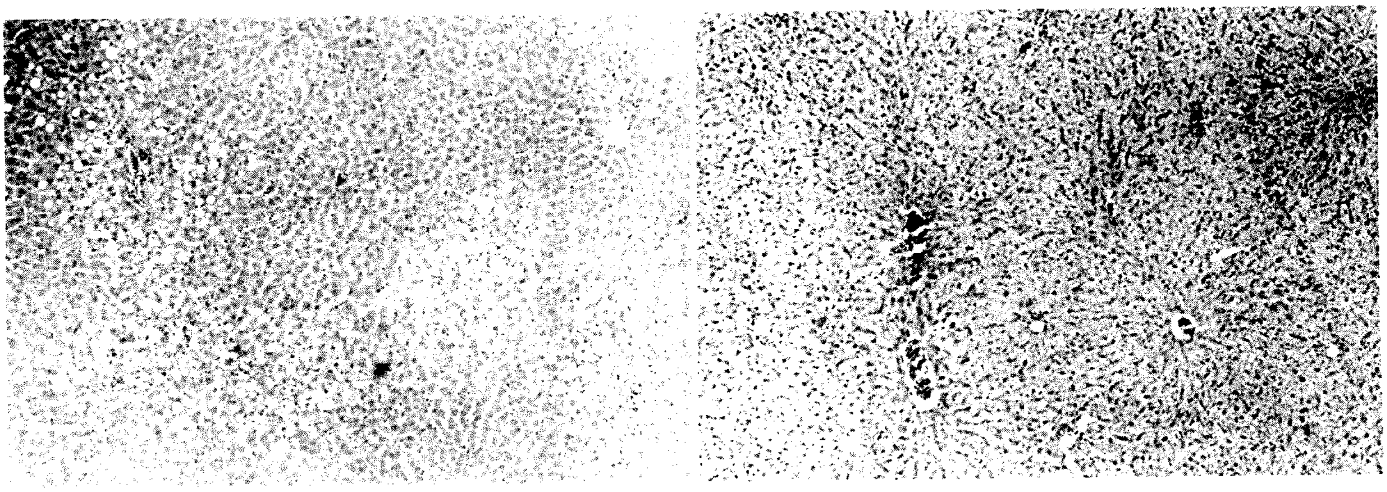

FIG. 3. Protein and calorie deprivation by 5% dextrose feedings in Group III rats resulted in mild periportal fatty infiltration in the intravenous animal (left) and normal appearing hepatic architecture in the oral rats (right). Further studies have shown that fatty infiltration does not always occur with the intravenous administration of a 5% dextrose solution.

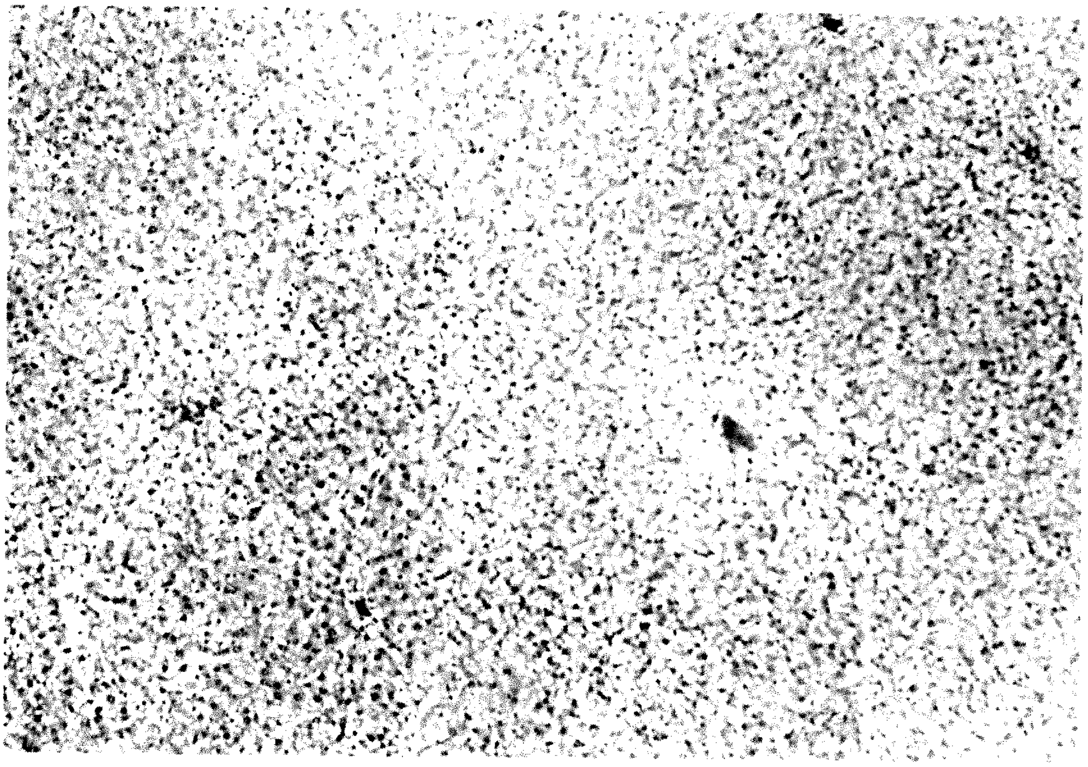

FIG. 4. Oral administration of 30% dextrose and water produced moderately severe fatty livers.

albumin levels to 2.5 gm % prior to the infusion of 30% dextrose. Even in healthy rats the intravenous administration of hypertonic dextrose without amino acids proved deleterious to serum albumin metabolism. If protein deprivation causes a decreased catabolism of intravascular albumin, then the lowered albumin levels in the intravenous 30% dextrose animals must be due to decreased albumin synthesis, perhaps secondary to massive fat accumulation in liver cells. The oral 30% dextrose group ingested an average of 12 calories per day less than their intravenous counterparts ($p < 0.05$); their serum albumin levels, however, were significantly higher, possibly reflecting less hepatic fatty infiltration. Although caloric intake was extremely low in the intravenous 5% dextrose

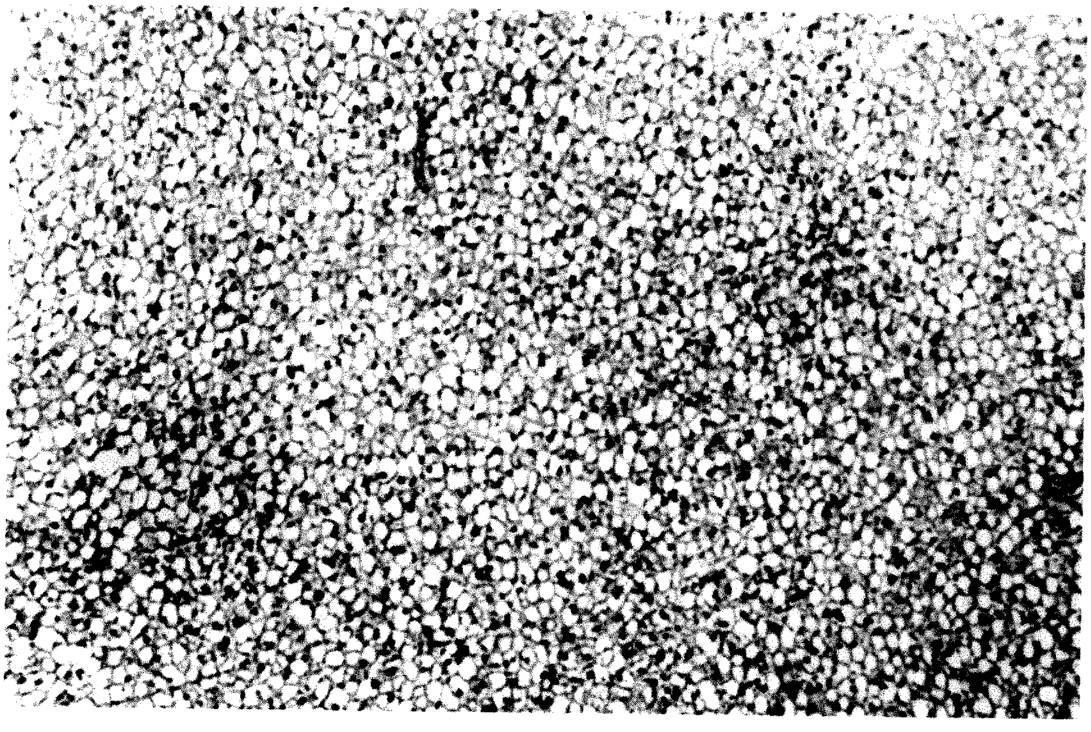

FIG. 5. Severe generalized fatty infiltration and vacuolization markedly distorts the normal hepatic morphology in all animals infused with a high calorie amino acid-free solution.

animals, serum albumin levels were comparable to their oral counterparts and to the oral 30% dextrose animals which received significantly more calories per day. Although these animals were semi-starved, infusion of 5% dextrose and water appeared to allow "sparing" of intravascular protein stores.

In this experiment, total circulating serum albumin correlated well with serum albumin levels. In contrast, however, to the findings of Sachar *et al*,[17] total circulating serum albumin did not correlate with body weight loss quantitatively, but did reflect nutritional status qualitatively.

Wound Healing

Clinically and experimentally, protein malnutrition has been shown to adversely affect wound healing.[9,14,18] A previous experiment from this laboratory demonstrated that a relationship exists between colonic wound healing and nutritional status in rats that were protein depleted for varying intervals.[4] The deleterious effects of protein deprivation on colonic wound healing have been shown to be reversed by the intravenous infusion of high calorie-amino acid solutions postoperatively.[18] Both the intravenous and oral administration of 30% dextrose-5% amino acids in this study allowed the greatest colonic anastomotic strength, nearly identical in magnitude. These results correlate with those of Moss and Koblenz[13] who demonstrated that biopsied wounds in dogs fed intravenously or by gastrostomy had comparable amino acid specific activities. Hypertonic dextrose, orally and intravenously, and oral 5% dextrose administration resulted in significant decreases in colonic anastomotic strength. Infusion of 5% dextrose resulted in moderate, though not statistically significant, reductions of anastomotic bursting strength. Thus, there was no correlation noted between caloric intake and colonic wound healing. The bursting strengths of segment 2 (proximal adjacent segments of colon) were not significantly different among the six groups of animals. Cronin *et al.*,[3] demonstrated that the highest synthetic and catabolic rates of collagen metabolism occurred nearest the anastomotic site. In this experiment, anastomotic bursting strength better reflected postoperative nutritional therapy than did a segment of colon not containing the anastomosis.

Hepatic Morphology

Loss of liver protein and hepatic fatty infiltration have been observed during the development of protein deficiency. Wang *et al.*,[21] found that liver nitrogen in rats decreased from 0.28 gm to 0.20 gm after seven days on a low choline, protein-free diet. In their animals, hepatic triglyceride content increased from 0.3 gm to 0.7 gm and bromsulfalein clearance decreased significantly. Hepatic fatty infiltration was distributed mainly in the periportal areas and was microscopically rated ++/+++. Best *et al.*,[1] demonstrated the association between centrilobular hepatic fatty infiltration and choline deficiency in rats. In their experiments, however, choline supplementation in protein-depleted rats did not prevent hepatic periportal fatty infiltration. Previous experiments in our laboratory demonstrated that intravenous infusion of 30% dextrose-5% amino acid solutions mobilized hepatic fat in rats previously fed a protein-free diet for six weeks.[18] Infusion of 5% dextrose and water into protein depleted animals also promoted fat mobilization from the liver, while 30% dextrose administration resulted in severe hepatic fatty infiltration.

In this experiment, the combination of the intravenous high calorie amino acid-free solution plus the absence of the lipotrophic agents choline or methionine produced extreme generalized hepatic fatty infiltration in a short period of time. Chang and Silvis[2] also noted moderate to severe hepatic fatty infiltration in rats receiving greater than 300 Cal/kg/day after four days of continuous infusion with hypertonic (20 to 25%) dextrose solutions. In our experiment, oral administration of the 30% dextrose diet resulted in moderate, predominantly periportal, fatty hepatic infiltration. Porta *et al.*,[15] suggest that increased synthesis of hepatic triglycerides from carbohydrate, increased output of free fatty acids from the fat depots, and impairment of triglyceride secretory mechanisms may be the cause of fatty liver in protein deficiency states. In Group II animals, the excess carbohydrate not utilized for energy needs most probably was shunted into fat synthesis, and impaired triglyceride secretory mechanisms resulted in hepatic triglyceride retention. The 5% dextrose groups demonstrate that the increased caloric load may be more important than the absence of lipotrophic substances as only minimal hepatic fatty infiltration was noted in these groups. Chang and Silvis,[2] using hypertonic dextrose infusion in normal rats, found that "addition of essential amino acids and arginine did not prevent the change (severe hepatic fatty infiltration), and protein hydrolysate seemed to minimize the fatty infiltration only at a lower caloric level (250 cal/kg/day), but not at high caloric levels (315 cal/kg/day)." In contrast, however, the intravenous and oral 30% dextrose-5% amino acid groups in our experiment received 335 and 265 cal/kg/day respectively. Histological examination of liver sections from these groups demonstrated only minimal periportal fatty infiltration. An explanation for these conflicting results may reside in the different infusion periods studied, and the quality of amino acid infusates utilized.

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Role of Insulin as a Portal Factor in Maintaining the Viability of Liver

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The subcutaneous administration of insulin did not induce a significant effect on oxidative phosphorylation of the mitochondria from normal rat liver. However, in rats subjected to ligation of a branch of portal vein, the phosphorylative activity of the mitochondria from the ligated lobe deprived of portal blood fell rapidly and at 12 hours decreased to approximately 50% of nomal liver mitochondria. After the insulin administration, the phosphorylative activity of the mitochondria from ligated lobe was rapidly stimulated within 30 minutes, reached the maximal level of normal liver mitochondria at 2 hours ($p < 0.005$) and then fell to subnormal levels. The respiratory control ratio, state 3 respiration and P/O ratio remarkably increased in parallel with an increase of phosphorylative activity. The contents of respiratory enzymes making up ATP remained unchanged. Considering the previous report that a factor, which is capable of stimulating oxidative phosphorylation of the liver mitochondria, is present in portal blood, it is suggested that insulin may play an important role in the mechanism by which the portal blood controls mitochondrial metabolism.

THE FUNCTIONAL STATUS of the liver is dependent upon portal blood supply. It is well recognized that, although it prevents the bleeding from varices of the upper gastrointestinal tract with decompressing the portal venous system, a portacaval shunt results in progressive deterioration of hepatic function. Bekoe *et al.*[1] have reported that derangement of liver mitochondria is more severe in the end-to-side shunted animals than in the side-to-side shunted animals and a major factor in initiating hepatic insufficiency following portacaval shunt. More recently, studies from our laboratory have shown, using portacaval shunted animals subjected to ligation of a branch of portal vein, that a portal factor, which stimulates the mitochondrial phosphorylative activity, is present in portal blood[9] and contributes significantly to maintain the delicate energy balance in damaged liver and the ability of the liver to regenerate.[3] It has been suggested that rapid alteration in mitochondrial metabolism in response to changes in portal blood supply is mediated by quantitative changes of the portal factor available to liver mitochondria. The role of the portal factor, however, in the control of liver mitochondria under physiological conditions remains conjectural. In this study, evidence will be presented that insulin plays an important role in the mechanism by which the portal blood controls the mechanism of liver mitochondria.

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Methods

Adult male rats of the Wistar strains weighing 150–200 gm were used in this investigation. Operations were carried out on rats under ether anesthesia. The left branch of the portal vein was ligated. In this way about 60% of the hepatic tissue was deprived of its portal blood supply. Insulin (crystalline, 0.35 units/mg, Sigma) was subcutaneously injected at the dosages indicated in the text simultaneously with intragastric injection of 400 mg of glucose per 200 gm of body weight. Liver mitochondria were prepared by the method of Ozawa *et al.*[8] Oxygen consumption was measured polarographically with a rotating electrode according to the method previously described.[7] Phosphorylative activity was measured simultaneously with oxygen utilization by following the changes in pH with glass electrode. For the assay of respiratory enzymes of liver mitochondria, the spectrophotometric techniques are described elsewhere.[8] Protein

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TABLE 1. *Changes of Oxidative Phosphorylation of the Mitochondria in Normal Rat Liver after Insulin Administration*

	Glutamate				Glutamate + Succinate			
	RC	State 3	P/O	PR	RC	State 3	P/O	PR
Control	4.7 ± 0.1 (8)	46.8 ± 0.9	2.3 ± 0.05	108.0 ± 5.5	5.2 ± 0.1	81.5 ± 0.9	1.8 ± 0.005	148.5 ± 8.1
Insulin	4.3 ± 0.3 (6)	58.5 ± 0.8	2.1 ± 0.1	124.3 ± 7.0	4.3 ± 0.3	85.2 ± 3.2	1.7 ± 0.1	158.9 ± 12.1

Values are means and standard errors. Values in parenthesis indicate number of animals. Oxygen consumption and phosphorylative activity were measured at 22 C at pH 7.4 in medium containing 0.3 M mannitol, 0.01 M KCl, 0.004 M $MgCl_2$, 0.01 M Tris-HCl buffer, 0.005 M potassium phosphate buffer, and 0.2 mM EDTA. Glutamate and succinate were added at a concentration of 4 mM. The respiratory control ratio was calculated from the polarographic tracings by the method of Chance[2] from the equation, RC ratio = state 3 respiration rate (in the presence of ADP)/state 4 respiration rate (after exhaustion of ADP). State 3, state 3 respiration (mμatoms/mg protein); P/O, moles of ATP formed per atom of oxygen consumed. PR, phosphorylation rate per mg protein (mμmoles ATP synthesis/mg/minute).

was determined by the method of Lowry *et al.* with crystalline bovine serum albumin as standard.[6]

Results

Table 1 shows the rates of oxidative phosphorylation of liver mitochondria of normal rats 2 hours after the administration of 2.5 unit per kg of insulin. In the respiratory control ratio, state 3 respiration, P/O ratio and phosphorylative activity, significant differences were not observed between insulin-treated and non treated rats. The findings raise the possibility that *in vivo* concentration of endogenous insulin reaching liver via portal system may be present in sufficient excess so as not to be rate limiting and to permit a maximal increase in the capacity for oxidative phosphorylation. Thus, in order to exclude the effect of endogenous insulin, a part of liver (ligated lobe) was deprived of portal blood supply with ligation of a branch of portal vein and used as a model for studying the mechanism of insulin action in more closely physiological conditions.

The phosphorylative activity of liver mitochondria rapidly fell after ligation of a branch of portal vein and at 12 hours was decreased to approximately 60 mμmoles ATP synthesized/mg protein/minute with glutamate as a substrate at 22 C, which were constantly maintained throughout the period studied (Fig. 1, a dotted line). From the results, the ligated lobe deprived of portal blood for 24 hours was used as a material.

Figure 2 shows the changes in phosphorylative activity of the mitochondria from ligated lobe 2 hours after the administration of various amounts of insulin. The phosphorylative activity of mitochondria from ligated lobe was remarkably stimulated to that of normal liver mito-

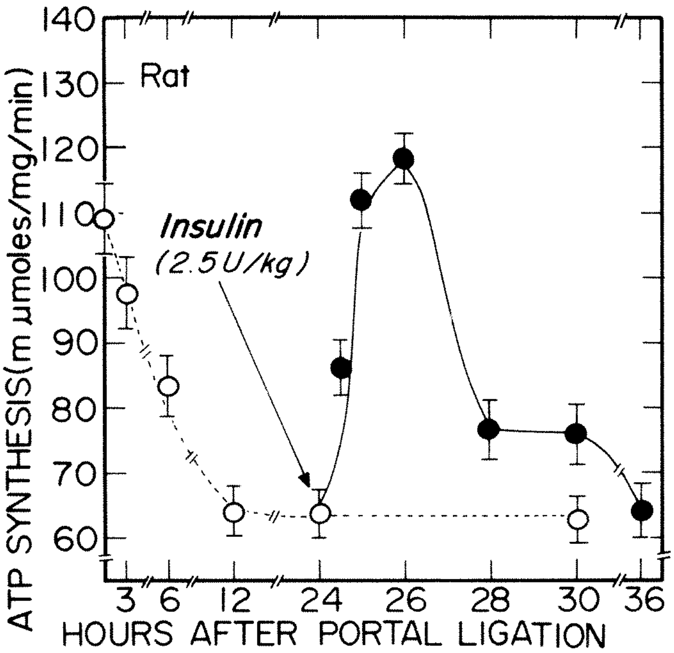

FIG. 1. Time course of changes of phosphorylative activity after ligation of a branch of portal vein (dotted line) and after insulin administration (solid line). Experimental details are given in Table 1. Each point represents the mean and standard error of values for eight or more animals.

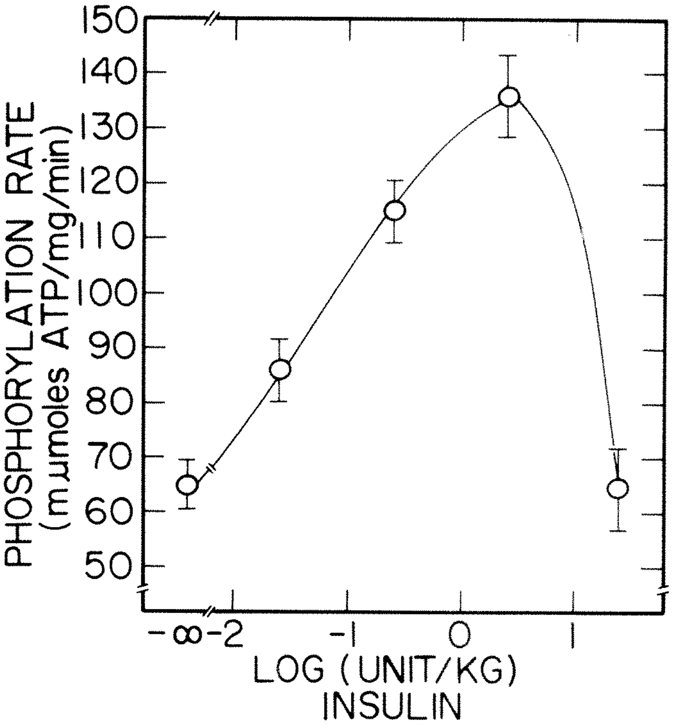

FIG. 2. Dose-response curve of insulin in phosphorylative activity of mitochondria of ligated lobe. Experimental details are given in Table 1. Each point represents the mean and standard error of values for eight or more animals.

TABLE 2. *Changes of Oxidative Phosphorylation of the Mitochondria in Ligated Lobe after Insulin Administration*

Hours after Insulin Administration	Glutamate				Glutamate + Succinate			
	RC	State 3	P/O	PR	RC	State 3	P/O	PR
Control	2.5 ± 0.1	34.3 ± 2.5	1.8 ± 0.08	62.0 ± 2.7	2.7 ± 0.1	79.7 ± 1.5	1.2 ± 0.05	98.0 ± 1.5
0.5	3.5 ± 0.2	44.5 ± 2.6	1.9 ± 0.04	87.0 ± 7.2	4.3 ± 0.02	108.0 ± 2.8	1.5 ± 0.03	164.0 ± 0.01
1	4.5 ± 0.3	51.8 ± 3.2	2.1 ± 0.1	108.4 ± 6.7	4.4 ± 0.1	117.5 ± 3.4	1.3 ± 0.04	155.0 ± 5.4
2	4.5 ± 0.2	52.0 ± 1.5	2.2 ± 0.05	114.8 ± 3.8	4.4 ± 0.2	108.9 ± 4.2	1.6 ± 0.06	175.4 ± 4.3
4	4.0 ± 0.1	42.0 ± 0.9	1.9 ± 0.08	80.1 ± 2.7	3.5 ± 0.1	96.8 ± 3.1	1.3 ± 0.05	122.7 ± 7.2
6	3.5 ± 0.2	44.2 ± 3.1	1.9 ± 0.06	83.2 ± 3.6	4.1 ± 0.2	89.5 ± 4.9	1.3 ± 0.05	116.0 ± 2.5
12	3.3 ± 0.1	31.7 ± 1.2	2.3 ± 0.04	71.8 ± 2.6	3.6 ± 0.2	80.6 ± 3.9	1.4 ± 0.02	117.0 ± 4.1

See footnotes to Table 1.

chondria with the administration of 0.25–2.5 unit per kg of insulin. The higher and lower concentrations did not result in a significant effect.

The changes of phosphorylative activity occurring in the mitochondria from ligated lobe following the administration of 2.5 unit per kg of insulin is shown in Fig. 1 (a solid line). The phosphorylative activity was rapidly stimulated within 30 minutes after the administration of insulin, reached 200% of control at 2 hours ($p < 0.005$) and then fell to subnormal level. The short period of maximal phosphorylative activity following insulin administration is an important characteristic of the physiological action. The respiratory control ratio, state 3 respiration and P/O ratio were maximally increased in parallel with an increase of phosphorylative activities with glutamate or glutamate plus succinate, as shown in Table 2. However, the contents of respiratory enzymes making up ATP remained unchanged (Table 3). On the other hand, 2 hours after the administration of glucose only the oxidative phosphorylation with glutamate as a substrate was slightly stimulated, possibly due to an increase in plasma insulin concentration occurring after glucose loading[4] (Table 4).

Discussion

It has been found in this laboratory that the interplay between a factor in portal blood and phosphorylative activity of liver mitochondria constitutes an important aspect in the excellent homeostasis for generation of energy.[3,9] The results presented herein indicate that, in an experimental *in vivo* conditions, insulin can enhance the mitochondrial phosphorylative activity depressed with portal deprivation. In addition, more recent studies showed that incubation of slices of the liver deprived of portal blood supply with insulin causes maximal enhancement of the phosphorylative activity of the mitochondria, but incubation with glucagon is without effect.[13] Although a number of factors might be involved in the mechanisms, it is clear that liver mitochondrial metabolism is, at least, regulated by an intrahepatic mechanism which is directly responsive to circulating insulin concentration. Considerable experimental evidences showed that insulin exerts multiple biological action.[15] However, there are no reports to show that regulation of mitochondrial phosphorylative activity is the fundamental physiological action of insulin. Also, at present, not enough is known regarding the regulatory action of insulin to interpret the observed responses. However, the mechanism of a beneficial effect of insulin on liver mitochondrial metabolism is a striking contrast to an increase of mitochondrial respiratory and phosphorylative activities following the administration of thyroid hormone. Tata[16] has concluded that a primary physiological effect of thyroid hormone is to increase biosynthetic processes controlling enzymes or structural elements of respiratory activity. An enhancement of oxidative and phosphorylative activities following the insulin administration appears to be due to different mechanism, since the contents of respiratory enzymes remain unchanged. The stimulated effect of insulin on mitochondrial metabolism appears to be localized at any single rate-limiting step of either the electron transport or phosphorylation

TABLE 3. *Changes of the Contents of Respiratory Enzymes after Insulin Administration*

	$a(+a_3)$	b	$c + c_1$	fp	PN
		10^{-10} moles/mg protein			
Normal Liver (6)	2.22 ± 0.08	0.92 ± 0.08	2.50 ± 0.06	7.2 ± 0.2	51.9 ± 1.6
Control (24 hours-ligated lobe) (8)	1.91 ± 0.09	0.82 ± 0.09	2.24 ± 0.06	8.3 ± 0.3	61.6 ± 2.6
Insulin-treated (24 hours-ligated lobe) (8)	2.13 ± 0.15	1.17 ± 0.05	3.12 ± 0.05	8.2 ± 0.4	55.5 ± 3.0

Insulin of 2.5/kg was administrated 24 hours after ligation of a branch of portal vein. The mitochondria were prepared from the ligated lobe 2 hours after insulin administration.

TABLE 4. *Changes of Oxidative Phosphorylation of the Mitochondria in Ligated Lobe 2 Hours after Administration of Glucose Only or Glucose Plus Insulin*

	Glutamate				Glutamate + Succinate			
	RC	State 3	P/O	PR	RC	State 3	P/O	PR
Control	2.5 ± 0.1	34.3 ± 2.5	1.8 ± 0.08	62.0 ± 2.7	2.7 ± 0.1	79.7 ± 1.5	1.2 ± 0.05	98.0 ± 1.5
Glucose	4.0 ± 0.3	39.5 ± 1.0	2.1 ± 0.07	83.0 ± 4.1	3.3 ± 0.1	82.7 ± 2.7	1.2 ± 0.02	101.6 ± 2.3
Glucose plus Insulin	4.5 ± 0.2	52.0 ± 1.5	2.2 ± 0.05	114.8 ± 3.8	4.4 ± 0.2	108.9 ± 4.2	1.6 ± 0.06	175.4 ± 4.3

See footnotes to Table 1.

system. The increase in the respiratory control ratio and P/O ratio suggests that a regulatory device such as conformational change in respiratory enzyme system participates in these mechanisms.

It is well recognized that portacaval shunting results in progressive deterioration of hepatic function. It is tempting to speculate that in the patients with decrease of portal flow rate (advanced liver cirrhosis) or diversion of the portal supply from the liver one of the most important causes for liver insufficiency is a reduction of insulin level per hepatic cell. This implies a basic defect in mitochondrial energy production which results in hepatic insufficiency, because hepatic cell metabolism is strongly dependent on the continuous supply of high energy phosphate mainly produced with the mitochondria. On the other hand, considering that redirecting the pancreatic venous drainage to the systemic circulation prevents the destruction of a major fraction of the secreated insulin and more insulin is available for the peripheral tissues, LeVeen *et al.*[5] have suggested that redirecting the pancreatic venous blood from the portal circulation to the systemic circulation dramatically alleviates the diabetes. However, since reduction of insulin concentration available to hepatic cell is not adequate to maintain functional integrity of hepatic cells, more studies appear to be required to apply such operation clinically.

Current investigations in this laboratory are concerned with elucidating metabolism of liver mitochondria in various liver diseases.[10,11] More recently, it has been found that, in the patients with liver cancer localized to one lobe, the phosphorylative activity of the mitochondria from tumor-bearing lobe is inhibited, while that from the lobe without cancer is enhanced.[12] Also, it has been found that in the mitochondria from regenerating liver of rat treated by chloramphenicol the oxidative and phosphorylative activities per unit of respiratory carriers are remarkably increased inversely with decreasing contents of cytochrome a($+a_3$), b and c_1.[14] Those indicate the presence of an excellent homeostatic mechanism in maintaining the delicate energy balance in liver. Insulin may play an important role in this mechanism. Further studies are under way.

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Carcinoid Tumors of the Gastrointestinal Tract

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The charts of 135 patients with gastrointestinal carcinoid tumors diagnosed over a 22-year period at 2 hospitals are reviewed and the clinical and pathological aspects discussed. Carcinoids occur most commonly in the appendix, jejunoileum, and rectum. Those smaller than 1 cm in diameter provide evidence of malignant potential only occasionally; lesions in the 1–1.9 cm range do this quite variably, and tumors 2 cm and larger are almost always invasive or metastatic or both. All gastrointestinal carcinoids except those of the appendix enlarge, invade, and metastasize predictably if given sufficient time. Most carcinoids except those of the rectum have already been adequately treated surgically when diagnosed by the pathologist. Local excision is effective treatment for non-invasive rectal carcinoids smaller than 2 cm in diameter, but those that have invaded or grown to 2 cm should undergo more radical resection. In general, gastrointestinal carcinoids carry better prognoses than do adenocarcinomata, and even in the presence of distant metastases long-term survival occurs in a significant number of patients. The frequent concomitance of associated malignant diseases accounts for as many or more deaths in these patients than the carcinoids themselves.

SINCE THE FIRST DESCRIPTION by Lubarsch in 1888[3] and Oberndorfer's[9] synthesis in 1909 of the term "carcinoid," 3,718 cases of carcinoid tumors have been described.

The carcinoid tumor or argentaffinoma is thus an uncommon tumor which contains a rich store of the tissue hormone 5-hydroxytryptamine (serotonin) which is produced by the argentaffine or Kulchitsky cells of the gastrointestinal tract. Carcinoids have been described in the stomach, duodenum, gallbladder, pancreas, in the lung, and in ovarian and testicular teratomata as well as at all levels of the gastrointestinal tract. The appendix is one of the common sites where the tumor presents as a yellowish mass at the appendicular tip, and though the tumor at this site may show local invasion histologically, it is generally benign in its course.

Carcinoids may be incidental findings at laparotomy or at autopsy. In the gastrointestinal tract, the tumor commences in the submucosa and extends outwards gradually involving the serosa, subsequently extending into the mesentery and adjacent structures. The tumor grows very slowly so that even with distant metastases many patients survive for long periods of time. The overlying mucosa usually remains intact, although occasional ulceration may occur. Only rarely does the tumorous mass encroach on the lumen, but annular constricting lesions may occur resulting in obstruction.

A review of our experience with carcinoids of the gastrointestinal tract provides 135 cases for study.

Materials and Methods

One hundred and sixty-one patients with carcinoid tumors of the gastrointestinal tract were seen at Charity Hospital and the Veterans Administration Hospital in New Orleans from 1948 to 1970. Five patients were excluded from analysis because of insufficient information. Twenty-one patients represented carcinoid-islet cell tumors of the duodenum that had been previously and separately studied[14] and were not further considered. The resulting 135 cases were composed of 115 from Charity Hospital and 20 from the Veterans Administration Hospital.

To determine the natural history of carcinoid tumors at specific sites in the gastrointestinal tract, the carcinoids were grouped according to location and mode of discovery as shown in Table 1. Included in this series are 35 patients with rectal carcinoids upon which a previous report was based.[2] We found no patient with carcinoids

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TABLE 1. *Location and Method of Discovery of 135 Carciniod Tumors of the Gastrointestinal Tract*

Location	Clinical	Autopsy	Total
Rectum	37	0	37
Appendix	27	2	29
Jejuno-ileum	18	19	37
Duodenum	8	4	12
Stomach	8	2	10
Colon	8	2	10
Total	106	29	135

of the esophagus, gallbladder, pancreas, or Meckel's diverticulum.

Attention was directed mainly to the charts of the 106 patients whose carcinoids were diagnosed clinically, and symptoms, method of diagnosis, treatment, pathologic features, and coexisting diseases were noted. The 29 carcinoid tumors discovered at postmortem examination were incidental findings and had produced no clinical symptoms. These cases were included only when pathologic features and the presence of coexisting disease were considered.

The carcinoid tumors were categorized according to size under one of three headings: 1) Less than 1 cm; 2) One to 1.9 cm; and 3) Two cm or larger.

The appropriate size of tumor was obtained from the description recorded by clinicians, surgeons or pathologists. The definition of size appeared important, and a search was made for correlation between tumor size, the presence of symptoms and extent of the disease process.

Followup information was available for 102 of the 106 clinical patients and was provided by outpatient clinic reports or Tumor Registries.

Results

Age and Sex

The average age of patients with appendicular carcinoids was 26 years, but ranged 45–55 years of age for the remainder of the 106 patients. There were no significant sex differences, the slight variations encountered being related rather to the composition of the patient populations of the two hospitals or by the nature of the operative procedures leading to the diagnosis.

Symptoms, Diagnosis and Treatment

Rectum. Symptoms referable to the rectum were present in 23 of the 37 patients with rectal carcinoids. These symptoms were caused by carcinoids in only 10 of the patients and were related to tumor size and extent as shown in Table 2. None of the 25 patients with carcinoid tumors smaller than 1 cm had symptoms attributable to their tumors.

TABLE 2. *Symptoms and Tumor Characteristics in the 12 Patients with Rectal Carcinoids One Centimeter in Diameter or Larger*

Symptoms	No.	Tumor Characteristics
Decreased stool calibre	4	Large proliferative masses
Rectal bleeding	3	Ulcerative lesions
Rectal pain	3	Infiltrating tumor
None	2	Small, no ulcerations or invasions

TABLE 3. *Treatment for the 37 Patients with Rectal Carcinoids*

Treatment	
Biopsy only	19
Biopsy with fulguration	4
Local excision	3
Anterior resection	1
A-P resection	10
	37

Rectal carcinoids were palpable on digital examination in 22 (59%) patients and visualized sigmoidoscopically in 34 (92%). In three patients with small lesions the tumors were undetected by either means. A microscopic diagnosis of carcinoid was made on 29 biopsy specimens, four of these confirming tentative clinical diagnoses. The carcinoid tumors were typically described by examiners as firm, smooth, yellowish submucosal nodules. An erroneous microscopic diagnosis of carcinoma was made on biopsies from 5 patients so that rectal carcinoids were either missed or mis-diagnosed in 8 patients (22%).

The modes of therapy applied to the 37 patients with rectal carcinoids are demonstrated in Table 3. Abdominoperineal resections were carried out in 10 patients and in 5 the original histologic diagnosis had been that of carcinoma. They were subsequently re-classified as carcinoids after completion of the operation. In four patients the presence of synchronous concomitant anorectal carcinoma determined the need for abdominoperineal resection. In only one patient was an abdominoperineal resection carried out for the specifically stated purpose of curing a carcinoid tumor of the rectum.

Jejuno-ileum. Symptoms in the 18 surgical patients with carcinoid tumors of the jejunum or ileum are categorized in Table 4. None of the patients presented with symptoms of the carcinoid syndrome. Abdominal masses were noted clinically in 6 patients who underwent operation. Three of these were attributable to intussusception and in 2 the masses were due to the matting of bowel loops. In only

TABLE 4. *Signs and Symptoms in 18 Surgical Patients with Jejunoileal Carcinoids*

Intestinal Obstruction		12
Acute:	5	
Chronic:	7	
Palpable mass:		6
GI bleeding		2
Asymptomatic		4
Total		18

1 patient was the primary tumor itself large enough to be clinically palpable.

An accurate preoperative diagnosis of acute intestinal obstruction was made in 5 patients. In the 7 patients with chronic partial obstruction vague abdominal complaints were of minimal diagnostic aid and a preoperative diagnosis of an underlying bowel tumor was not made in any of these cases. X-ray studies with contrast media were positive for intestinal obstruction in 2 patients but did not provide an accurate diagnosis of the underlying carcinoid tumor.

In the 12 patients with varying degrees of obstruction only one carcinoid was larger than 2.5 cm in diameter and this represented the only palpable primary tumor. This was a 6 cm tumor arising in the terminal ileum and invading the cecum. Luminal occlusion by the bulk of the primary lesion was not apparent in any of the other 11 patients with obstruction. In three patients the mechanism of obstruction was attributable to intussusception. The mechanism of obstruction was not overtly related to the primary lesion in the other eight patients in whom large mesenteric metastases, the presence of mesenteric fibrosis, or kinking and matting of bowel loops provided the pathogenetic basis for the intestinal obstruction (Fig. 1).

Resection of small bowel and mesentery was carried out in all 18 surgical patients. In 6 patients the right colon was resected en-masse with the terminal ileum. In 14 cases the operating surgeon was unaware that a carcinoid tumor was present in the resected specimen, while in the other 4 patients frozen sections were obtained and provided immediate and accurate diagnosis.

Stomach and Duodenum. There was 8 patients with gastric and 8 patients with duodenal carcinoids providing a total of 16 with gastroduodenal carcinoids who underwent surgical therapy. Upper gastrointestinal bleeding was a prominent feature in all 8 patients with gastric tumors and occurred in 4 patients with duodenal lesions. In each of these 12 patients, either an ulcer or an ulcerative mass was found. The gastroduodenal symptoms were usually attributable to coexisting disease, i.e. peptic ulcer or gastric carcinoma, rather than to the carcinoid tumor per se. There were associated gastric ulcers in 4 patients and duodenal ulcers in 7, the carcinoid being found in the base of the ulcer crater in most.

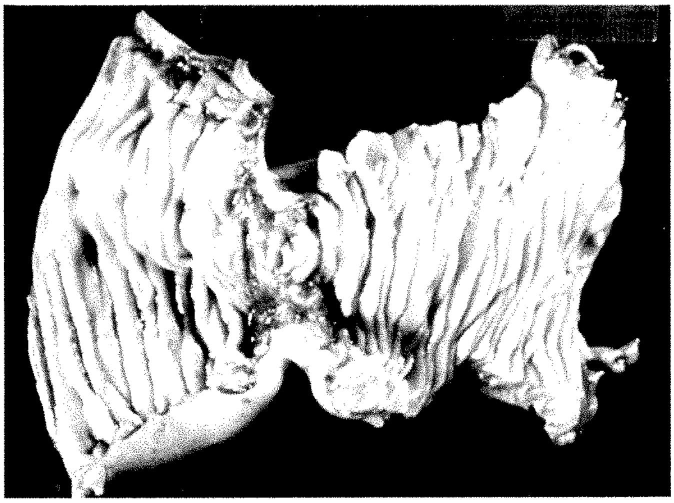

FIG. 1. Carcinoid of jejunum with narrowing of lumen induced by fibrosis causing subacute obstruction.

Gastric analysis was performed in 3 patients and in none was hyperchlorhydria present. Endoscopy and barium contrast studies were accurate in establishing the presence of associated pathologic processes, but the carcinoid tumors were diagnosed preoperatively in only 2 patients with polypoid lesions.

Treatment consisted of 14 gastric resections for ulcer or carcinoma, actual or suspected; one pancreatoduodenectomy for an invasive tumor of the second portion of the duodenum; and one local excision of a polypoid tumor of the duodenal bulb. This latter case represented the only carcinoid tumor diagnosed intraoperatively.

Colon. Carcinoid tumors of the colon occurred in 8 surgical patients, 6 of whom were symptomatic. The symptoms are categorized in Table 5 and strongly resemble those attributable to the more commonly encountered adenocarcinoma. Palpable lesions were present in 2 patients. Four tumors were demonstrated preoperatively, 1 by proctoscopy and 3 by barium enema. Four were first discovered at laparotomy, 2 for obstruction, 1 for perforation, and 1 during an elective cholecystectomy. All the tumors were thought clinically or operatively to be carcinomatous except the one within reach of the sigmoidoscope. Appropriate resections of right or left colon were performed.

Appendix. In 27 patients the diagnosis of carcinoid tumor was made after appendectomy. The procedure was performed for appendicitis in 17 patients and as an incidental procedure in 10. In 6 cases the tumors were located in the proximal half of the appendix in patients who presented with appendicitis and it is conceivable that the tumor was of etiologic importance in causing the symptoms. In the other 21 patients the distal location of the tumors excluded a role in the pathogenesis of appendicitis nor could any symptoms be attributed to them.

Appendectomy alone was the treatment for appendiceal carcinoids in all but two patients. One underwent a subsequent negative "second-look" laparotomy, and a right hemi-colectomy was performed in the other. Neither residual tumor nor metastasis was found in the resected specimen.

Surgical extirpation was the sole mode of therapy in the 106 patients in the clinical series. None received adjuvant chemotherapy or palliative irradiation for carcinoid tumor. A palliative hepatic resection was performed in 1 of the 2 patients who developed the malignant carcinoid syndrome. These two patients did not manifest symptoms attributable to the syndrome when the intial diagnosis of a carcinoid tumor was made and surgical treatment instituted, but presented with symptoms and biochemical findings of the carcinoid syndrome 5 or more years after treatment of the primary lesion.

TABLE 5. *Symptoms in 8 Surgical Patients with Carcinoid Tumors of the Colon*

Anemia	1	
Weight loss	1	
Large bowel obstruction	3	
Acute:		2
Chronic:		1
Perforation	1	
Asymptomatic	2	
Total	8	

Extent of Disease

The relationships between extent of disease in terms of local invasion as well as nodal and distant metastases in 135 patients with carcinoid tumors in this series are categorized in Table 6. The tumor size at each affected level of the gastrointestinal tract is appropriately tabulated. A tumor was considered invasive when it had infiltrated to or beyond the muscularis propria. The liver was involved in all patients who had distant metastases, and tumor implants were frequently found also in the parietal peritoneum, omentum, mediastinum, or spinal cord. No metastases to lung, brain, or bone were encountered in this series.

It is noteworthy that among the 37 patients with rectal carcinoids there were two patients with carcinoids smaller than 1 cm in diameter who presented with metastases to the regional nodes in the absence of muscularis invasion. These two cases have been previously recorded and considered by Genre *et al.*,[2] but it is necessary to explain the apparent paradox of patients in the rectal group having more distant than regional nodal metastases. This is attributable to the fact that resection was not performed in several patients whose distant metastases were discovered at exploration so that the status of regional nodes was unknown.

We have classified carcinoid tumors as being malignant when either muscular invasion and/or metastases were found. Fifty of the series of 135 cases (37%) were thus defined as being malignant carcinoids. Of the 106 patients in the clinical group, 43 (41%) had carcinoids which qualified for malignant status, in distinction to the autopsy series where only 7 (24%) were malignant.

It was apparent in this study that the larger the tumor the more likely its malignant propensity. At each level of the gastrointestinal tract there was a correlative relationship between those lesions that were 1 cm in diameter or larger and the presence of malignant characteristics. This relationship is demonstrated in Table 7.

TABLE 6. *Extent of Disease in 135 Patients with Gastrointestinal Carcinoids*

			Overt Malignancy			Pathologic Features	
						Metastases	
Location	Size	No.	No.	%	Invasive	Nodes	Distant
Rectum	Less than 1 cm	25	3	12%	1	2	0
	1–1.9 cm	6	3	50%	2	0	2
	2 cm or larger	6	5	83%	5	1	4
	Total	37	11	30%	8	3	6
Jejuno-ileum	Less than 1 cm	20	6	30%	6	1	0
	1–1.9 cm	12	12	100%	12	8	2
	2 cm. or larger	5	5	100%	5	5	5
	Total	37	23	62%	23	14	7
Stomach	Less than 2 cm	5	0	0%	0	0	0
	2 cm or larger	5	5	100%	5	5	3
	Total	10	5	50%	5	5	3
Duodenum	Less than 2 cm	10	0	0%	0	0	0
	2 cm or larger	2	2	100%	2	2	1
	Total	12	2	17%	2	2	1
Colon	Less than 1 cm	1	0	0%	0	0	0
	1–1.9 cm	2	2	100%	2	1	1
	2 cm or larger	7	7	100%	7	7	6
	Total	10	9	90%	9	8	7
Appendix	Less than 1 cm	29	10	34%	10	0	0

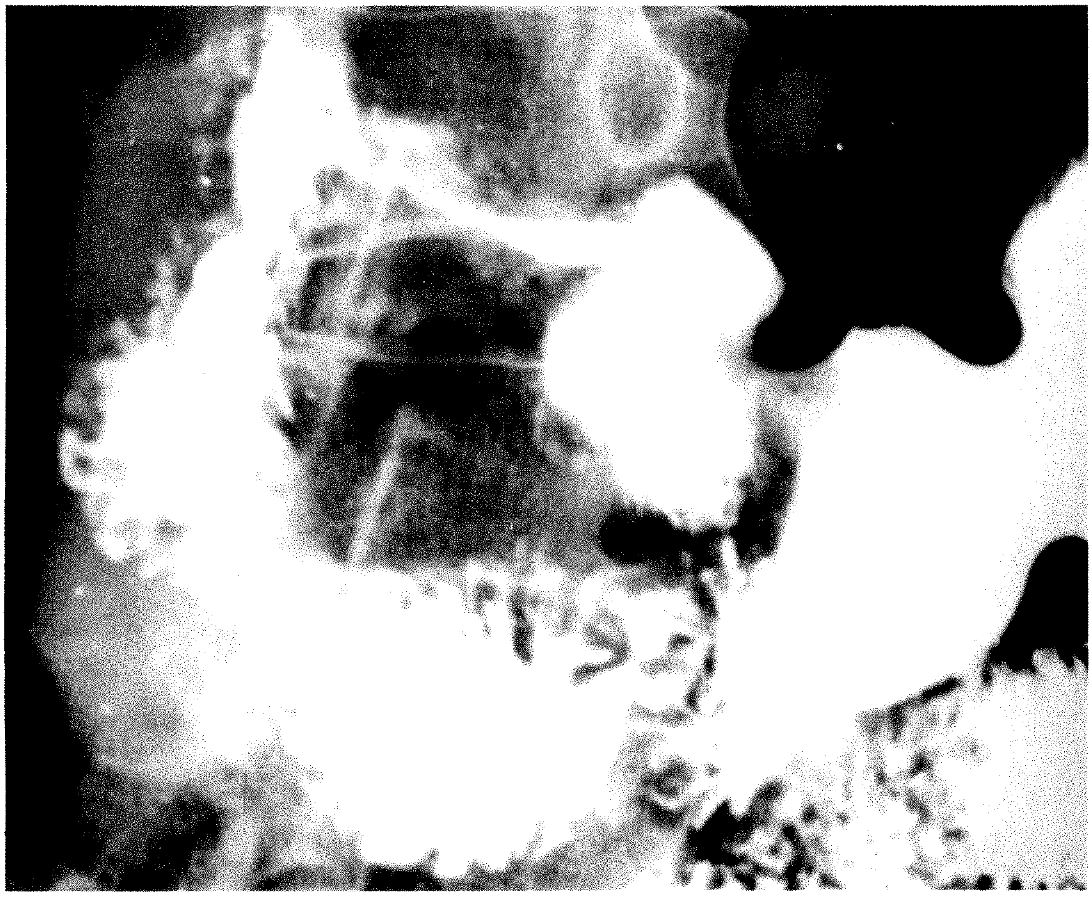

FIG. 2. Gastric filling defect discernible on barium study due to gastric carcinoid.

Site Distribution

The distribution of carcinoid tumors within their respective locales in the gastrointestinal tract is shown in Tables 8 and 9. It is of interest that the middle third of the rectum, i.e. 5–8 cm from the anal verge, provided the locus for 57% of the rectal carcinoids, and 50% of this group demonstrated malignant features. Forty three percent of the rectal carcinoids were sited in the proximal and distal thirds of the rectum, but malignant features were present in only 7% of this group.

Multicentricity

Carcinoids were found to be multiple in 40% of patients with jejunoileal tumors and in 8% of patients with rectal lesions. Multiplicity was not a feature of carcinoids in other locations.

TABLE 7. *Variable Effect of Size on Malignant Propensities (Tumors Greater than 1 Cm)*

Location	No.	Tumor: 1 cm + No.	Tumor: 1 cm + %	Overt Malignancy No.	Overt Malignancy %
Colon	10	9	90%	9	90%
Jejuno-ileum	37	17	46%	23	62%
Stomach	10	6	60%	5	50%
Rectum	37	12	32%	11	30%
Duodenum	12	3	25%	2	17%

Associated Malignant Neoplasms

It is noteworthy that although patients with colon carcinoids did not have associated malignant neoplasms, such an association occurred at every other site (Table 10).

The Carcinoid Syndrome

Significant elevations of urinary 5-hydroxyindoleacetic acid were found in 1 of 4 patients with hepatic spread from gastric carcinoids, in 2 of 6 patients with rectal carcinoids metastatic to liver, and in 2 of 7 patients with

TABLE 8. *Rectal Carcinoids: Level of Involvement*

Level (cm)	No.	Malignant Features
11	1	0
10	5	1
9	3	0
8	3	2
7	6	4
6	7	2
5	4	2
4	3	0
3	1	0
2	2	0
Unspecified	2	0
	—	—
Total	37	11

TABLE 9. *Extra-Rectal Carcinoids: Site Distribution*

Jejuno-ileum (37)	
Jejunum	5
Ileum	29
Jejunum & Ileum	3
Stomach (10)	
Antrum	10
Duodenum (12)	
1st portion	10
2nd portion	2
Colon (10)	
Cecum	5
Descending colon	1
Sigmoid	4
Appendix (29)	
Base	2
Mid	4
Tip	23

hepatic metastases from jejunoileal carcinoids. The latter 2 were the only patients in the entire series manifesting the malignant carcinoid syndrome.

High levels of urinary 5-HIAA were also noted in one patient with a localized duodenal carcinoid. After excision of the duodenal carcinoid the level of 5-HIAA returned to normal.

Elevations of 5-HIAA were not seen in any of 9 patients with liver metastases from duodenal and colon carcinoids.

Survival

Of the 106 patients in the clinical series, 102 were followed. There was 5-year followup for 85 (83%) of the 102, the other 17 being alive and free of clinical disease less than 5 years. Ten-year data were available for 70 patients, and both the 5-year and 10-year survival figures are shown in Table 11.

It is interesting that all 18 patients in the jejunoileal group had tumors with malignant characteristics. Of the 11 patients whose rectal carcinoids were designated as malignant, 9 qualified for 5-year followup, only 2, or 22%, surviving 5 years or more. Two of the 6 patients dying of metastatic rectal carcinoid had tumors in the 1–1.9 cm range.

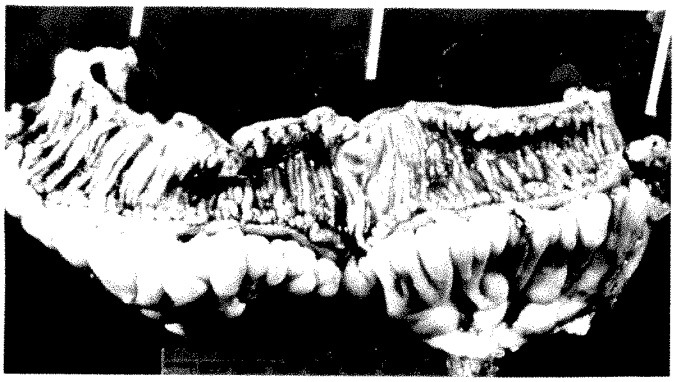

FIG. 3. Multiple carcinoid tumors within single jejuno-ileal segment.

TABLE 10. *Associated Malignant Neoplasms*

Site	No.	%
Rectum (37)	12	32
Jejuno-ileum (37)	14	37
Stomach (10)	2	20
Duodenum (12)	3	25
Colon (10)	0	0
Appendix (29)	4	13
Total (135)	35	26

Of the 24 patients with carcinoids metastatic to liver, 5 (21%) survived 5 years and 4 of these survived 10 years. The primary tumors were jejunoileal in 3 and of colon origin in 2. None of the 6 patients with hepatic metastases from rectal carcinoids survived 5 years.

No patient with an appendiceal carcinoid died of the disease and none developed evidence of recurrence or metastasis.

Discussion

Pathology

Lubarsch[3] demonstrated by serial sections that carcinoid tumors begin in the mucosal crypts of Lieberkuhn, and more specifically, Masson,[4] using silver staining techniques, showed their origin to be from the Kulchitsky cell. The affinity for silver stains led to the term argentaffin tumors but this histochemical phenomenon is neither specific for carcinoids nor consistently present, and is not necessary for their identification.

Many carcinoids are the size of a match head, most are no larger than a dime,[1] while a few exceed a diameter of 2 cm. They appear grossly and microscopically in a submucosal position even though they originate in the mucosa. They are composed of small cells, uniform in size and occurring in various patterns,[1] but neither cellular morphology nor histologic pattern can be used to distinguish the aggressive lesions.

Their expansion is usually horizontally within the submucosa as well as away from the lumen. The more aggressive lesions, having penetrated the wall of the viscus of origin, can invade mesentery, parietal peritoneum, and other organs. Metastases, when present, are usually to regional lymph nodes and liver and only occasionally to other distant sites such as lung, brain, and bone.

Lubarsch[8] thought these tumors to be malignant and called them "little carcinomas" to differentiate them from the ordinary adenocarcinoma. By 1907, however, most of the few discovered lesions had been found to be localized, and Oberndorfer[9] confidently emphasized their benign and harmless character and coined the term "carcinoid." In 1949, Pearson and Fitzgerald[11] reviewed the first large series of gastrointestinal carcinoids and found metastases in 38% of non-appendiceal cases and recommended that all carcinoids be considered malignant.

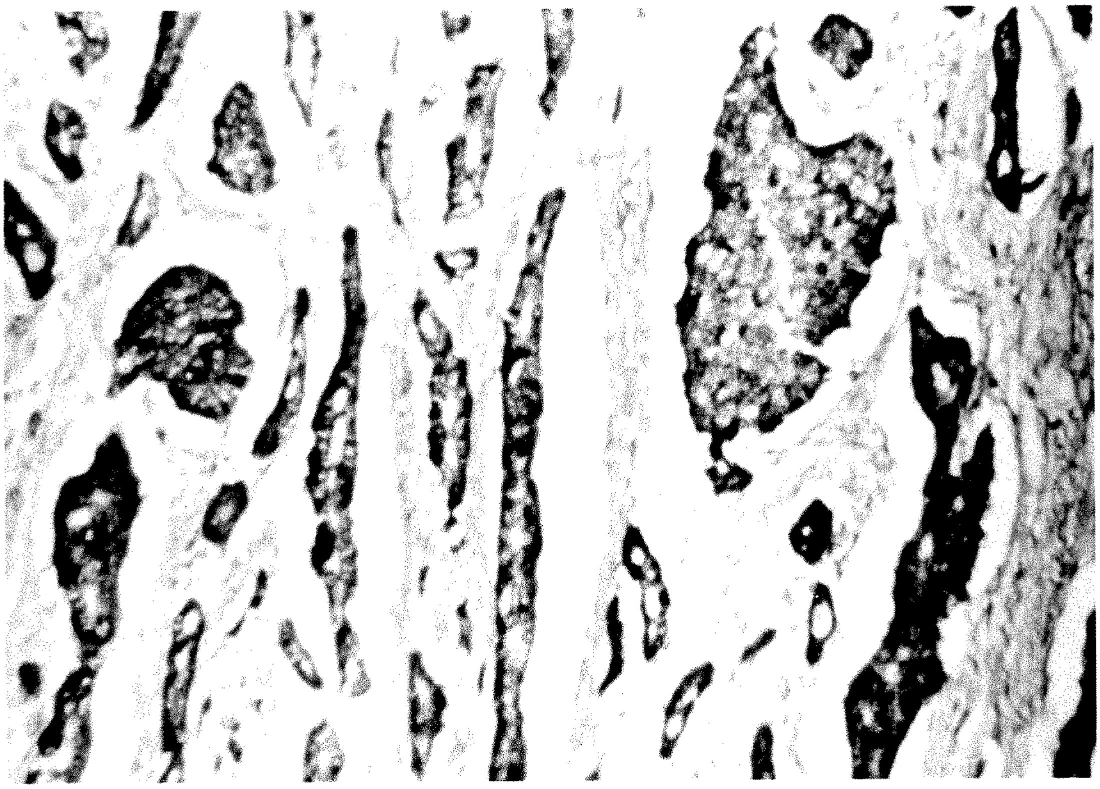

FIG. 4. Microscopic appearance of carcinoid with wavy strands and argentaffin positive columns of cell (×240).

McDonald[5] in 1956 was the first to propose an index of malignancy exclusive of known metastases. In a classic paper describing a large series of gastrointestinal carcinoids, he noted muscular invasion in all but one case of those extra-appendiceal carcinoids that had metastasized and suggested that carcinoids be reported by pathologists in terms of invasiveness. Peskin and Orloff[12] and Orloff,[10] in their study of rectal carcinoids, demonstrated a striking correlation between size and malignant behavior. They noted a 4% incidence of metastasis (and invasion) for tumors less than 2 cm in diameter in contrast to 80% (invasion, 93%) for lesions 2 cm or larger. Our findings (Table 6) support such a relation between size or invasiveness on the one hand and the occurrence of metastases on the other for all extra-appendiceal carcinoids. Furthermore, according to our data, the aggressiveness of those extra-appendiceal tumors in the 1–2 cm range approaches or equals that of the larger lesions.

Symptoms

Carcinoid tumors of the stomach, duodenum, appendix, and rectum are usually asymptomatic, symptoms related to associated diseases often leading to their incidental discovery.

Carcinoids of the large and small intestine usually provide symptoms, although for each the complaints may vary from vague and longstanding to dramatic and acute. Symptoms of colon carcinoids are indistinguishable from those of adenocarcinoma, and those beyond the reach of the sigmoidoscope will usually be diagnosed as carcinoma by barium enema or at laparotomy.

Symptomatic jeunoileal carcinoids cause acute or chronic intestinal obstruction. A small intramural jejunal or ileal carcinoid does not readily obstruct the bowel lumen but may serve as an intussusceptum. More commonly, the bowel may be kinked by neoplastic or fibrotic distortion of the mesentery, the primary tumor itself being

TABLE 11. *Survival of 85 Patients with Carcinoid Tumors*

		5 Year Data			10 Year Data			
Site	No.	Qualify	Survival	Per cent	Qualify	Survival	Per cent	Dead of Carcinoid
Rectum	37	30	14	46%	25	9	35%	6
Jejuno-ileum	18	14	8	57%	11	5	45%	4
Stomach	8	8	4	50%	7	3	43%	3
Duodenum	8	6	4	66%	4	2	50%	1
Colon	8	6	2	33%	6	2	33%	4
Appendix	27	21	17	80%	17	13	76%	0
Total	106	85	49	58%	70	34	49%	18

inconspicuous. McNeal[6] postulated that a carcinoid, by continued intramural lateral expansion after invasion and attachment to the muscularis, causes serosal indentation, kinking of the bowel, and apposition of adjacent serosal surfaces. Later, the fibrotic reaction commonly accompanying carcinoid tumors completes the adhesive and obstructive process.

Diagnosis and Treatment

Carcinoid tumors of the stomach, duodenum, jejunoileum, and colon are usually first defined as carcinoids by the pathologist a day or two after an operation in which significant and appropriate portions of the involved organ and its lymphatic drainage routes have been resected for other disease, real or suspected. Consequently, surgeons rarely plan therapy for these lesions and are willing to accept what has been done as adequate, and justifiably so.

For appendiceal and rectal carcinoids, however, a different situation is presented. Carcinoids of the appendix are also diagnosed postoperatively by the pathologist, but in this case the surgeon is confronted with the question of advisability of re-operation. There are contemporary proponents of an aggressive approach in the treatment of appendiceal carcinoids, but the most conservative and seemingly the most authoritative opinion is given by Moertel *et al.*[7] in their definitive paper based on the study of 144 cases. All had invaded muscularis, lymphatic invasion was present in 98%, and the serosa was involved in most. Despite this consistent local invasiveness, they found metastases in only 2 of the 3 lesions 2 cm or larger in diameter. Their categoric statement that simple appendectomy is adequate for all lesions except those with gross evidence of invasion or those greater than 2 cm in diameter reflects our view.

The rectal carcinoid is the only carcinoid which can be seen, felt, and diagnosed without a major surgical procedure. In most instances the therapeutic alternatives, as in the case of villous adenoma, are simple local excision or the more formidable abdominoperineal resection.

Peskin and Orloff,[2] in 1959, first proposed criteria for the choice of treatment in patients with rectal carcinoids. They emphasized the importance of obtaining a specimen, by biopsy or excision, adequate for microscopic examination for muscular invasion. In the presence of such invasion radical resection was recommended, while in its absence local excision would be deemed sufficient. Because of their observation of a precipitous increase in the incidence of muscular invasion and/or metastasis when rectal carcinoids attained a size of 2 cm or greater, they suggested that radical resection be seriously considered for these larger lesions even if invasive features were absent. Recently Orloff[10] re-affirmed these criteria and reported a 76% 5-year survival rate resulting from the application of these therapeutic principles.

Associated Malignant Neoplasms

The high incidence of associated malignant neoplasms in patients with carcinoid tumors has been known since Pearson and Fitzgerald's discovery of this occurrence in 23% of autopsy cases.[11] This association was more frequent in our patients than is usually reported,[1,10] particularly in the rectal group, for which we found an incidence of 32%. Another interesting finding in our series was that the associated malignant diseases were responsible for more deaths than the carcinoids.

Survival

Carcinoid tumors of the appendix carry an excellent prognosis, while the outlook is poorest for patients with colon carcinoids. The prognosis for patients with other gastrointestinal carcinoids is reasonably good, the 5-year survival rates in our series varying from 46% to 66%.

Shorb and McCune[13] referred to the long-term survival that can be expected in patients with gastrointestinal carcinoids, even in the presence of recurrence or metastases, and they emphasized the value of palliative resections for these patients. Wilson[15] has reported the benefits of palliative hepatic resection for symptomatic metastatic carcinoids, and, of our 24 patients with hepatic metastases, 2 underwent successful hepatic resections, and 21% of the total survived 5 years.

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Hypothermic Asanguineous Circulatory Arrest in Adult Dogs

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A new technique for the institution of hypothermic asanguineous circulatory arrest (HACA) is described and evaluated. It employs rapid cooling and hemodilution at high flow rates. Survival and protection of neurologic and other organ function were obtained using asanguineous circulatory arrest, and the method appears to be an improvement over circulatory arrest using conventional methods for cooling. The total duration of extracorporeal circulation is much shorter than with currently used methods of circulatory arrest. Applications of this technique in general and transplantation surgery as well as cardiac surgery are discussed.

IN RECENT YEARS, sanguineous solutions have been used with considerable success in *in vitro* organ preservation.[2,5,7,19] A report published in this journal from our laboratory[7] described a successful method for preservation of canine hearts for 24 hours using hypothermic asanguineous perfusion. The need for *in situ* multiple organ preservation of transplant donors, the use of asanguineous circulatory arrest in infants with congenital heart disease,[25] and the recent use of an asanguineous solution in total body washout for hepatic coma[12] stimulated the application of similar techniques to the problem of hypothermic circulatory arrest. A new method for rapidly instituting hypothermic asanguineous circulatory arrest (HACA) was devised. Periods of circulatory arrest in adult dogs which might be of use in adult patients for complicated thoracic or abdominal operations, or uncontrollable hemorrhage, were used. Evaluation of the method, its limitations, and its effects on the physiology and anatomy of adult dogs was undertaken. Improvement upon previously reported time limitations[13,18] and survival rates[18,22] was obtained.

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Methods

Fifteen adult mongrel bitches weighing 19.4 ± 6 kg (mean ± 1 SE) were anesthetized with intravenous sodium thiamylal, 15 mg/kg, and halothane. Ventilation was maintained through a cuffed endotracheal tube. Dogs were placed on large bags of crushed ice (Fig. 1) and given 30 mg/kg methylprednisolone and 500 ml of 6% Nasopharyngeal and either esophageal or middle ear temperature, electrocardiogram, arterial and central venous pressures, urine output (through a Foley catheter placed in the bladder), pH and blood gases, hemograms, and blood chemistries were monitored. Urine sodium, potassium, creatinine, urea nitrogen, and osmolality were measured serially in six dogs. In five dogs, pre- and postoperative phothrombin time, partial thromboplastin time, thrombin time, and fibrinogen were measured.

In five dogs, a high fidelity micromanometer pressure transducer* was placed in the left ventricular chamber through the apex, and an electromagnetic flow transducer† was placed on the ascending aorta enabling measurements of left ventricular pressure, left ventricular dp/dt, left ventricular Vmax (theoretical maximal velocity of contraction), stroke volume and cardiac output.

The Krebs solution used was formulated as follows: NaCL 6.92 gm/L, KCl 0.35 gm/L, $CaCl_2$ 0.7 ml of the 20% hydrated solution/L, KH_2 PO_4 0.16 gm/L, $MgSO_4$ $7H_2O$ 0.29 gm/L, glucose 2.0 gm/L, $NaHCO_3$ 2.1 gm/L, dextran (MW 70,000) 6 gm/L. The osmolality was 290

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* Model P-22 Konigsberg Instruments, Pasadena, California.

† Series 5000, Biotronex Laboratories, Inc., Silver Spring, Maryland 20910.

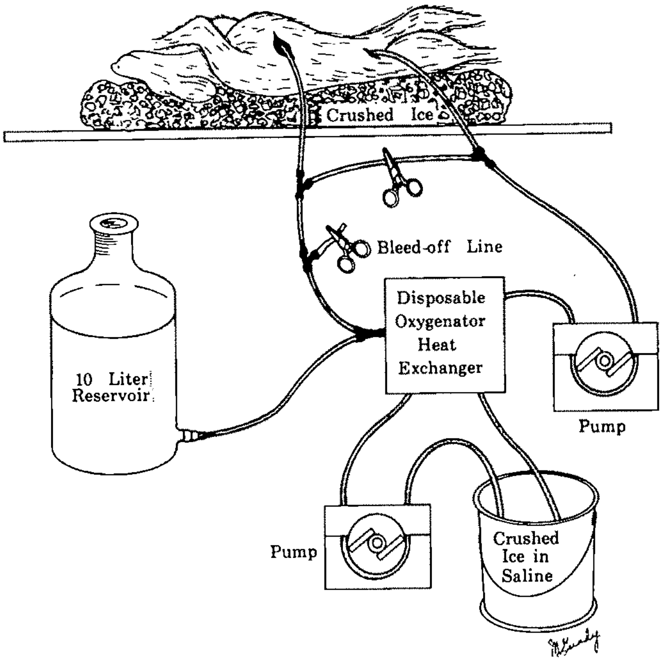

FIG. 1. Perfusion circuit for hypothermic asanguineous circulatory arrest. Large volumes of cold Krebs solution could be delivered rapidly using the 10 liter reservoir.

mOsm/L. Ionic concentrations were as follows: Sodium 148 mEq/L, potassium 6.2 mEq/L, Chloride 122 mEq/L, carbon dioxide 18 mEq/L, calcium 4.2 mg %, and magnesium 5.0 mEq/L.

Cold Krebs solution was precirculated through the disposable oxygenator-heat exchanger* (Fig. 1). Iced saline delivered through a second pumping circuit was used to cool the heat exchanger. After systemic heparinization (2 mg/kg) and cannulation of the femoral artery (14 Fr. catheter) and the right atrium (32 to 34 Fr. catheter) through a thoracotomy (13 dogs had a right thoracotomy, 2 had a left thoracotomy), the cooling period was begun. Oxygenated (98% O_2, 2% CO_2 at 7 L/min), cold (0–3 C) Krebs solution (usually a total of 24 liters per dog) was pumped at about 200 ml/kg/min into the arterial line from a 10 liter reservoir. The entire venous return was collected in large sterile flasks. Care was taken never to distend the heart. Pump flow, arterial pressure, central venous pressure, and temperature was monitored at one minute intervals. The washout was continued until the nasopharyngeal temperature fell below 10 C (usually 4 to 8 minutes). Core temperature, as measured by middle ear or esophageal probe, fell more rapidly. The circulation was then arrested for 46 to 180 minutes (Table 1). Fluid balance was 200 to 300 ml positive. Prior to rewarming, the ice bag under the dog was removed, the first 8 L of dilute blood removed during the washout period was warmed to 37 C for later readministration and the oxygenator was refilled with fresh heparinized whole blood which passed through a precirculating loop and the oxygenator-heat exchanger.

The rewarming period began with another exchange transfusion lasting from 4 to 8 minutes. At flows of 80 ml/kg/minute ,the 8 liters of previously collected dilute autologous blood were pumped into the arterial circulation while the venous return was discarded. Samples from the initial venous return were taken as approximations of capillary level pH and blood gases. Recirculation of venous blood was then begun and warming proceeded at a slower rate (Fig. 2). Sodium bicarbonate (89 mg) and warm heparinized blood (usually 3 to 4 units) were added to the pump. Defibrillation was successful 10 to 30 minutes after the start of rewarming. Cardiopulmonary bypass was discontinued 5 to 10 minutes later and 5 ml of 10% calcium chloride was administered. Thoracotomies were closed, leaving a chest tube for drainage for several hours.

In the postoperative period, serial hemograms and blood chemistries were obtained. Animals with severe neurologic damage and failure to show signs of recovery by 2 to 5 days after operation were sacrificed. All dogs but one (still alive 6 monthe after operation) which survived the immediate postoperative period were later killed (Table 1) and subjected to a complete autopsy including the brain and thoracic and abdominal organs. Three of the animals surviving more than one month underwent cardiac catheterization with measurement of left ventricular pressure, left ventricular dp/dt, and duplicate dye dilution cardiac outputs.

TABLE 1. *Survival, Cause of Death, and Clinical Evidence of Brain Damage in Dogs after 46 to 180 Minutes of Hypothermic Asanguineous Circulatory Arrest*

Arrest period (min)	Survival Period (days)	Cause of Death	Brain Damage
46	11	Sacrifice	None
60	45	Sacrifice	None
90	>180	Alive	None
120	30	Sacrifice	None
120	30	Sacrifice	None
120	12 hours	Unknown	—
120	12 hours	Error (ET Cuff Leak)	—
120	2	Pneumonia	None
120	1½	Inadequate spontaneous ventilation	Mild
120	1	Inadequate spontaneous ventilation	Mild
120*	4 hours	Pulmonary edema	—
120*	4 hours	Pulmonary edema	—
150	6	Sacrifice	Severe
180	2	Sacrifice	Severe

* Left thoracotomy used.

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* Pediatric Model, Bentley Laboratories, Santa Ana, California 92707.

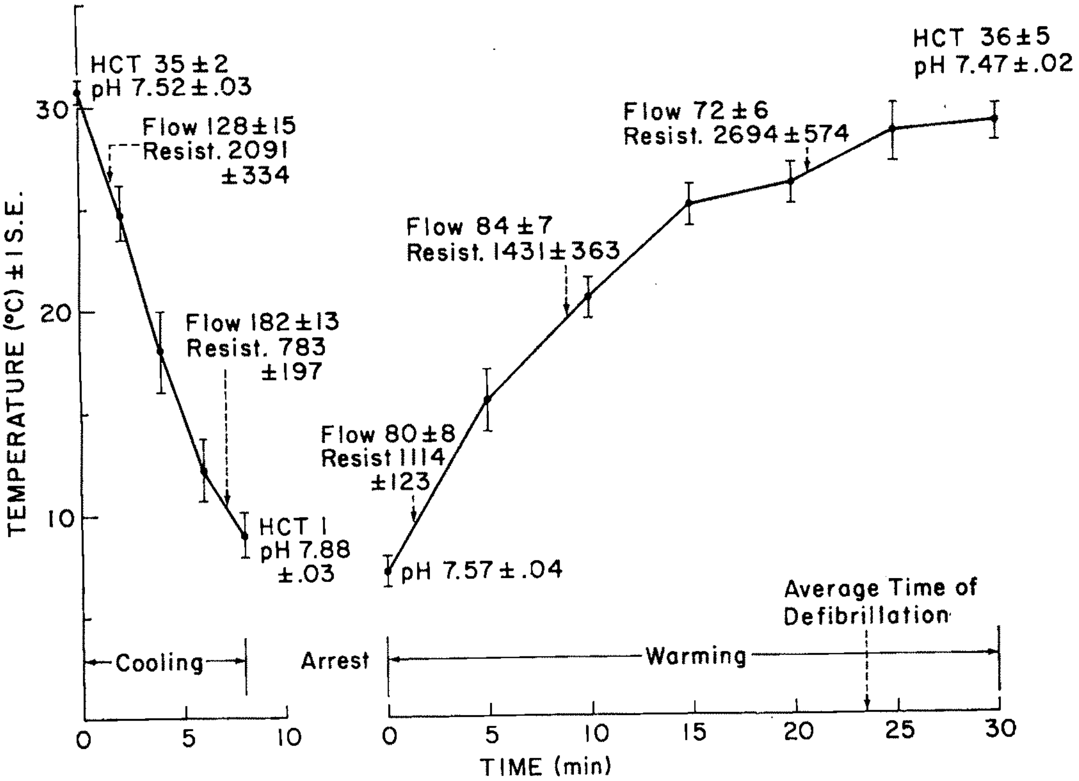

FIG. 2. Temperature (°C) with hematocritis (%), pH, total systemic vascular resistance (Resist.-dynes sec. cm.$^{-5}$), and pump flow (Flow-ml./kg/min) ± S.E. are shown during the cooling and rewarming period for all experiments.

Calculations

Total systemic vascular resistance during cooling and warming was calculated as follows:

$$\text{T. S. R.} = \frac{\text{Mean Art. Pr. (mm Hg)} - \text{Central Venous Pr. (mm Hg)} \times 80}{\text{Pump flow (L/min)}}$$

to give absolute resistance units (dynes sec cm^{-5}). Values were obtained shortly after the onset of cooling, at the end of the cooling period, at the beginning of warming, halfway between onset of warming and defibrillation, and just before defibrillation.

Blood gas[24] and pH[21] values were corrected for temperature. The values during profound hypothermia, however, are approximate, being derived from extrapolations of standard nomograms.

Calculation of Vmax was done by digital computer plotting of left ventricular dp/dt divided by the product of instantaneous ventricular pressure and the series elasticity modules K (28 per muscle length)[8] during the period of isovolumic systole and extrapolating the downslope of this curve to zero pressure.[15,27]

Results

Cooling from 31 C to 10 C required 6 to 7 minutes (Fig. 2) and was accompanied by a fall in hematocrit from 35 ± 2% to <1%. Nasopharyngeal temperature was generally slower in falling and rising than esophageal or middle ear temperature and was felt to be the best of the three in approximating brain temperature. The pH rose slightly from 7.52 ± .03 in blood at 31 C to 7.88 ± .03 in Krebs solution at less than 10 C, and there were falls in pO_2 from 270 ± 27 to 71 ± 5 mm Hg and pCO_2 from 28 ± 3 to 7 ± .6 mm Hg. During the cooling period the total peripheral vascular resistance fell from 2091 ± 334 to 783 ± 197 dynes sec cm^{-5} (63%) and the mean arterial pressure fell from 55 ± 5 to 29 ± 5 mm Hg. During circulatory arrest the temperature drifted downward 2–6 C. Rewarming from 7 C required 30 minutes, and defibrillation was accomplished an average of 23 minutes after the start of rewarming. In the last six animals, the addition of a second heat exchanger of higher efficiency in series with the first heat exchanger decreased rewarming time to 20 to 25 minutes and permitted defibrillation after 10 minutes. The hematocrit was brought to a normal level during this time. Fluid taken from the venous return line shortly after initial drainage was begun had a pH of 7.57 ± .04, a pO_2 of 9 ± 2 mm Hg, and a pCO_2 of 12 ± .6 mm Hg and was felt to represent "tissue level" pH, pO_2, and pCO_2. At the end of the warming period, dogs had a mean pH of 7.47 ± .02, pO_2 of 261 ± 31 mm Hg, and pCO_2 of 33 ± 1 mm Hg. Prior to defibrillation, total systemic resistance rose from 1114 ± 123 to 2604 ± 574 dynes sec cm^{-5} and mean arterial pressure rose to 48 ± 6 mm Hg. Serum sodium and potassium remained in normal range.

Survival

All three animals that underwent HACA for periods up to 90 minutes survived with no evidence of brain damage (Table 2). An animal subjected to 46 minutes of HACA had a palsy of the hind legs which lessened with time, as well as a third degree burn of one hip from a heating pad during the warming period. Because this burn became infected the animal was sacrificed 11 days after operation. Of the ten dogs subjected to 120 minutes of HACA, two died of pulmonary edema, apparently resulting from deleterious stretching of the ventricle during cooling and warming. Left thoracotomies were used in these two dogs and were abandoned after this experience. One other dog in this group died from a mechanical mistake (endotracheal tube cuff leak). Of the remaining seven dogs undergoing 120 minutes of HACA, six (86%) survived at least 24 hours. One died at approximately 12 hours after operation from unknown causes. Three of the six survivors had neurologic damage. Two had a gasping over-inflating breathing pattern and died one and one-half days following operation. The other dog had limited spontaneous activity (eating and drinking), ataxia, though able to move all extremities, and occasional tremors and was sacrificed six days after operation because of failure to improve. The three remaining dogs (43%) did not appear to have suffered neurologic damage. One of these died of pneumonia two days after operation, the other two survived until sacrifice (greater than 30 days).

After 150 to 180 minutes of HACA, survival was attained in two dogs, but neurologic damage was severe and consisted again of limited spontaneous activity (eating and drinking), ataxia, and tremors with no sign of improvement. These animals were killed two and six days after operation.

Postoperative Studies

A post bypass diuresis occurred in all animals. The urine was slightly concentrated (416 ± 47 m osm/L) containing 117 ± 23 mEq/L sodium and 26 ± 7 mEq/L potassium. Urinary urea and creatinine concentrations fell from 1080 ± 379 preoperatively to 174 ± 37 mg % postoperatively and from 115 ± 65 preoperatively to 14 ± 3 mg % postoperatively.

Postoperative bleeding, while not a problem, was in some cases greater than anticipated. In six animals, prebypass and post-bypass prothrombin times, partial thromboplastin times, thrombin times and fibrinogens were not significantly different. It was, therefore, felt that if an abnormality in hemostasis existed it might be due to the effect of dextran on platelet adhesiveness, but this question was not examined. Platelet counts after discontinuation of cardiopulmonary bypass were normal (174 ± 23 × $10^3/\text{mm}^3$).

Myocardial contractility in the early post-bypass period was normal to moderately greater than normal in five dogs. Maximal dp/dt rose from 2575 ± 415 mm Hg/sec in the first several minutes following bypass to 5850 ± 935 mm Hg/sec at one hour post-bypass (normal 2500).[27]

Vmax rose from 2.97 ± .55 circumferences/sec immediately following discontinuation of bypass to 3.53 ± .31 circs/sec at one hour post-bypass (normal 3.0 ± .07 circs/sec).[11,27] In the one animal studied one day following operation, these values were not significantly changed. Also, in three chronic survivors catheterized prior to sacrifice (approximately one month following surgery), the mean value for maximal dp/dt was 4008 ± 1233 mm Hg/sec.

TABLE 2. *Serial Mean White Blood Cell Count (cells × 10^3 per mm^3,) Hematocrits (%), and Platelet Counts (× 10^3 per mm^3) ± S. E. are given for Control, Postbypass (PBP), Postoperative Days 1, 2–4, 5–7, Two Weeks and One Month*

	White Blood Count × 10^3	Hematocrit	Platelets × 10^3	N
Control	8.4 ± 9	36 ± 2	160 ± 28	14
PBP	8.4 ± 1.4	34 ± 2	174 ± 23	16
POD 1	27 ± 3.4	43 ± 3	128 ± 22	11
POD 2–4	17 ± 1.7	42 ± 1	83 ± 23	7
POD 5–7	20 ± 3.2	33 ± 4	115 ± 30	7
2 weeks P. O.	19 ± 3.5	32 ± 3	102 ± 45	4
1 month P. O.	15 ± 1.8	40 ± 1	207 ± 59	4

N = Number of dogs.

Mean cardiac output in the immediate postoperative period in five dogs was 1.88 ± .42 L/min. In the three chronic survivors catheterized more than one month after operation, mean cardiac output was 4.83 ± 1.64 L/min. All postoperative measurements of left ventricular pressures were normal. Only the two dogs that had inadequate venous drainage (left thoracotomies), ventricular dilatation during cooling and warming, showed evidence of heart failure. No abnormal myocardial function was noted in any of the other dogs.

Laboratory Studies

Serial laboratory values are shown in Tables 2 and 3. White blood cell counts rose to 27± 3.4 × 10^3 cells/mm^3 on the first day after operation and fell gradually, not reaching normal levels by one month. Hematocrits remained in a relatively normal range (32 ± 6 to 43 ± 9%) for the length of the experiment. There was, however, a sharp drop in hematocrit at 4 to 7 days after operation and a rise did not occur again until one month after operation. This decrease coincided with a rise in total and direct bilirubin and in serum lactic dehydrogenase and probably represented hemolysis. Surprisingly, platelet counts were not significantly reduced from normal at any time in the experiment. Bilirubin rose modestly (1.56 ± .76 mg% at two weeks after operation) and fell to normal at one month postoperative. Similarly, serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and creatine phosphokinase (CPK) exhibited mild rises (Table 3) reaching peaks by one week and returning to normal by one month after operation. Serum glucose rose to abnormal levels (154 ± 61 mg%) only on the determination immediately following discontinuation of cardiopulmonary bypass. All subsequent mean values were normal. Mean serum protein values fell nearly 50% in the immediate postbypass

TABLE 3. *Serial Mean Values ± S. E. for Total Bilirubin (mg per 100 ml), Serum Alkaline Phosphatase (Alk. Phos. IU per 100 ml), Serum Glutamic Oxalacetic Transaminase (SGOT IU per 100 ml), Serum Glutamic Pyruvic Transaminase (SGPT IU per 100 ml), Serum Lactic Dehydrogenase (LDH IU per 100 ml), and Serum Creatine Phosphokinase (CPK IU per 100 ml).*

	Bilirubin Total	Alkaline Phosphatase	SGOT	SGPT	LDH	CPK	N
Control	.36 ± .04	21 ± 3	53 ± 5	27 ± 6	143 ± 21	256 ± 66	14
PBP	.30 ± .05	22 ± 2	186 ± 29	57 ± 11	240 ± 32	1010 ± 264	16
POD 1	.84 ± .11	122 ± 13	622 ± 34	180 ± 12	232 ± 24	1832 ± 943	11
POD 2–4	.76 ± .18	129 ± 28	222 ± 59	161 ± 11	184 ± 34	707 ± 148	7
POD 5–7	.87 ± .35	108 ± 19	115 ± 12	105 ± 15	431 ± 73	655 ± 193	7
2 weeks P. O.	1.56 ± .76	—	98± 11	52 ± 15	347 ± 69	365 ± 88	4
1 month P. O.	.50 ± .05	23 ± 9	64± 8	33 ± 10	309 ± 53	197 ± 38	4

N = Number of dogs.

period and subsequently were normal. Mean values for serum calcium, amylase, lipase, electrolytes, creatine and blood urea nitrogen were normal on all determinations for the entire experiment. There was no significant difference in serial laboratory values among dogs after 46–180 minutes of HACA.

Pathology

Examination of thoracic and abdominal organs at necropsy in all dogs failed to reveal any abnormalities. Subendocardial hemorrhage,[22] mucosal necrosis of the bowel,[22] and pancreatitis[18] have been reported following hypothermic circulatory arrest of 1 to 2 hours in dogs. Neither gross nor microscopic examination demonstrated any of these except in the case of hearts into which a micromanometer pressure transducer had been placed. In those hearts, focal subendocardial hemorrhage in areas immediately adjacent to the site of the left ventricular apical stab wound were found.

External inspection of all dog brains was normal. Gross inspection of the cut surfaces revealed no pathologic findings.

Discussion

A new technique for the induction of HACA was successful in rapidly (6–7 minutes) cooling dogs to below 10 C, while conserving the dog's own blood for later reinfusion. High flow rates (approx. 200 ml/kg/min) were used to make the cooling period as rapid as possible and to flush rapidly and cool all capillary beds. Total systemic resistance fell during the cooling period to 13% of the resistance found at the beginning of cooling. The hematocrit fell to less than 1% and the corrected value for pH rose ot 7.88 at the beginning of the arrest period. "Tissue level," pH, pO_2 and pCO_2 measured in samples taken from the venous discard line shortly after reperfusion with warm blood was begun were 7.57, 9 mm Hg and 12 mm Hg respectively. Normal values for pH, pO_2, and pCO_2 were found at the completion of rewarming and after discontinuation of cardiopulmonary bypass.

Survival was 100% for three dogs after 46, 60, and 90 minutes of HACA. After 120 minutes of HACA, four of seven dogs (57%) with right thoracotomies that did not die as a direct result of a mechanical error survived two days or more. Three of these had no evidence of permanent neurologic damage and two of these survived more than 30 days until sacrifice. After 150 and 180 minutes of HACA, neurologic damage was severe, but 100% survival occurred and evidence for cardiac, hepatic, renal, or pancreatic dysfunction was absent. These results compare favorably to those of Osteen[18] who had no dogs survive more than 11 hours after a 60-minute period of HACA. Other investigators[6,13] have reported good survival rates after 60 minutes of circulatory arrest when hemodilution was not used. Rush[22] reported survival for two days or more of 6 of 13 dogs (46%) after two hours of circulatory arrest again using whole blood rather than total body washout. Therefore, it appears that survival with this technique is better than that with a previous technique for total body washout,[18] and also slightly better than with techniques which did not use hemodilution.[22] Perhaps the most important reason for this improvement is the short exposure time of dogs to extracorporeal circulation. The mean duration of cardiopulmonary bypass in these experiments was 49 ± 3 minutes. When a second heat exchanger was added during the warming period the time on bypass was decreased to 41 ± 3 minutes. In the previously reported experiments,[13,18,22] the cooling period alone was as long as our total time of cardiopulmonary bypass. The ability to cool rapidly in this experiment resulted from perfusion with a large volume (24 L) of Krebs solution at high flow rates (180–200 ml/kg/min).

The advantages of using a completely asanguineous solution, besides providing an unlimited supply of perfusate are not well defined. It is, however, well known[2–5,7,19] that far greater success in *in vitro* organ preservation has been obtained with asanguineous solutions than with whole blood when combined with hypothermia.

With this technique it is clear that protection of the brain by cooling is of prime importance. Signs of permanent brain damage were found in three of six animals that survived 24 hours or more after 120 minutes of HACA and in the two animals that survived HACA for 150 and 180 minutes.

There was no functional, laboratory or necropsy evidence for dysfunction of any non-neurological organ in any of the survivors. Mild elevations of serum enzymes are expected after any surgical procedure. The absence of marked enzyme elevations suggested that no visceral organ necrosis was occurring. Pre- and postoperative tests of blood clotting were normal. These experimental findings are in accord with the findings of Lesage[13] who reported the results of circulatory arrest in 300 dogs. They are also in agreement with the clinical results of Belsey[1] who found no evidence of permanent neurologic or visceral damage in 304 patients ages 18 months to 65 years undergoing up to two hours of circulatory arrest.

The clinical use of hypothermic circulatory arrest at present is for the most part confined to open heart surgery in infants.[17,25,26] In the past, it has been used successfully by some in children and adults.[1,9,14] Other experiences[10] have been disastrous. Clearly, brain damage has been the factor which has limited the time period of arrest in both dogs[6,13,16,22] and patients.[10] The time limitation for circulatory arrest without permanent brain damage with our techniques appears to be between 90 and 120 minutes.

A technique very similar to ours, employing hemodilution to an hematocrit of 8%, has been successfully used in 25 infants in the correction of congenital heart defects.[25] Theoretically, however, our technique is best suited for situations in patients where rapid protection of the central nervous system and other organs with hypothermia and conservation of autologous blood are desirable, such as traumatic aortic aneurysms, hepatic trauma, massive hemorrhage, etc. The technique is simple, employing rapidly available equipment, and could be used in any institution where cardiopulmonary bypass is available.

A further possible use for this technique is in the field of organ preservation. Rapidly instituted HACA in donor candidates with irreversible brain damage in outlying hospitals would allow time for cadaver transport to transplantation centers where multiple organs could be obtained by various transplant teams. This also would minimize handling of organs and insure that organs were removed properly. Hypothermic preservation without continuous perfusion has been successful with kidneys for 72 hours,[23] with liver for 11 to 12 hours,[3] and with hearts for 24 hours.[20] Our experiments have demonstrated maintenance of normal function of all non-neurologic organs for three hours. Studies are presently underway to extend this time period.

Finally, our experiments suggest that anoxic damage during hypothermic total body washout for hepatic coma should not occur if the washout period is rapid and the estimated brain temperature is near 10 C.

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Perforative Carcinoma of Colon and Rectum

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As further statistical evidence accumulates it is becoming evident that a major factor in the differing patient salvage between perforative and uncomplicated cancer of the colon and rectum is the element of infection. The absence of abdominal sepsis is undoubtedly responsible for the lessened morbidity and mortality found in the treatment of established fistulas. Surgical attention should therefore be directed first to the eradication of the primary source of infection, the perforated tumor. The safety with which an intestinal anastomosis may be made in the presence of edema and inflammation is a matter of mature judgement on the part of the operating surgeon. Postoperative suture line leakage should be avoidable. Extirpative surgery with or without anastomosis, coupled with the judicious drainage of the peritoneal cavity, antibiotic coverage, and blood volume support should continue to give improved results in the management of this distressing complication of cancer of the colon and rectum.

THE COMPLICATIONS of cancer of the colon and rectum continue to provide some of the most difficult challenges in surgery today. There is still no unanimity of opinion as to the most effective methods of handling severe obstruction or perforation caused by these tumors; and the hospital mortality and long term survival of patients with these conditions are considerably less favorable than are those of uncomplicated carcinoma. As a followup of an earlier report from this institution[7] this study reviews the management and outcome of a group of patients with perforated colorectal cancer, encountered at the Massachusetts General Hospital over the years 1958 through 1970.

A review of the literature reveals that extended resection of locally spreading cancer of the colon is not new. At the Mayo Clinic, in a series of patients dating back to 1906, 20% of individuals in whom the colonic tumor was found fixed to the abdominal wall were cured after radical removal of the lesion with adherent parietal wall.[23] In more recent reports, attached organs such as the urinary bladder,[9,14,34] liver,[36] ovaries,[16] and small bowel[9,14,27] have been resected in continuity, along with the primary cancer. Indeed, such tumors on pathological examination often show certain features considered favorable to long-term survival; such as the finding of well-differentiated cancer cells, circumscribed, "pushing" type of inflammatory margins, and regional lymph nodes which are free of metastases.[3,27]

In contrast, carcinomas which have perforated through the intestinal wall to form local abscesses, and those which have perforated freely, resulting in peritonitis and diffuse sepsis, have been approached with much more conservatism. In 1957, in reporting a series of 115 patients with free perforation, only 22 of whom (19%) came to resection, Goligher and Smiddy[10] emphasized the hazards of conservative management and the high initial mortality associated with non-operative care. It has been only in recent years that more aggressive measures have been employed and found to result in improved survival. At the Massachusetts General Hospital there has been a steady rise in the rate of resection of perforative colorectal cancer from 47% in 1938–1942, to 70% in 1954–1958, to 79% in 1961–1965, and to 81% in 1966–1970. A resectability rate of 80% has also been recently reported by Glenn and McSherry.[9]

Method

Between 1958 and 1970, 2004 patients were admitted to the Massachusetts General Hospital with carcinoma of the colon or rectum, and of these 118 (5.9%) were found to be perforated, either at the time of surgery or at

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TABLE 1. *Adherent Structures Resected: 2004 Cases of Cancer of Colon and Rectum 1958–1970*

Organ	Cases	Mortality	5-Year Survival*
Ovary	51	2%	45%
Small bowel	31	10%	16%
Uterus	29	3%	43%
Bladder	16	6%	31%
Kidney	7	14%	33%
Prostate	6	17%	40%
Abdominal Wall	6	0%	40%
Other	18	11%	25%
Totals	164	6%	34%

* Complete 5 year followup, 1958–67.

autopsy. Perforation was defined as one of three types in which cancer cells and enteric contents had escaped from the intestinal lumen: 1) those rupturing freely into the peritoneal cavity; 2) those leaking locally, with formation of an abscess; and 3) those perforating into a nearby hollow viscus or to the skin, with creation of a fistula. In keeping with our previously published report, the microscopic findings of malignant cell spread or penetration through the serosa of the bowel, did not constitute a perforation. In the present series of cases, there are a considerable number of patients in whom adjacent organs were resected along with the colonic cancer because of adherence by either cancer cell penetration or inflammatory reaction (Table 1). This group of patients has been deleted from this study because of the difficulties and inaccuracies encountered in determining the exact nature of the adherence.

Seventy-three patients (62%) were female, and 45 (38%) were male. The average age was 69 years, only 6% of the group being less than 50 years of age, and 23% being more than 80 (Table 2). Abdominal pain was the most common presenting symptom, occurring in 60% of individuals. Other complaints included changes in bowel habits (35%), vomiting (20%), bleeding per rectum (12%), weight loss (14%), and abdominal mass (10%). The average duration of symptoms for the entire group was 7.6 weeks, and the median duration 6 weeks. Patients with free perforations presented with acute symptoms, and on occasion free sub-diaphragmatic air was evident on abdominal x-ray study. Their median duration of symptoms was found to be one week only, compared with 1.7 months in the case of perforation with abscess formation, and 2.5 months in those individuals who developed fistulas.

TABLE 2. *Age Distribution (118 Cases)*

Decades	Cases
20–29	1 (1%)
30–39	1 (1%)
40–49	5 (4%)
50–59	21 (18%)
60–69	27 (23%)
70–79	35 (30%)
80–89	25 (21%)
90–99	3 (2%)

TABLE 3. *Distribution of 120 Tumors (118 Cases)*

Cecum	19.0%
Ascending colon	2.5%
Hepatic flexure	6.6%
Transverse colon	10.7%
Splenic flexure	3.3%
Descending colon	6.6%
Sigmoid colon	32.2%
Rectosigmoid	13.2%
Rectum	5.8%

Approximately two-thirds of the tumors arose in the left colon, but unlike the distribution found in uncomplicated cancer, only 6% were found in the extra-peritoneal rectum (Table 3). Two patients each had two synchronal tumors. Of the total group, 51 patients (42%) presented with free perforation, and an identical number with abscess formation. Fistulas, either internal or external, were found in 18 individuals (15%). In the right and transverse colon, free perforations were found approximately twice as commonly as abscesses, and four times as frequently as fistulas. In the left colon, on the other hand, 50% of the patients with perforation presented with abscess formation, particularly in the sigmoid segment. Fistulas, surprisingly, were found in a similar percentage of cases (15%) in all three major subdivisions of the colon. More than half of the fistulas communicated with the small intestine, including 6 to the ileum, 2 to the duodenum, and 2 to the jejunum. Other sites of fistula formation were: adjacent colon—two, vagina—2, skin—2, uterus—1, and stomach—1. Two patients perforated freely into the peritoneal cavity at the site of a fistula (Table 4).

The site of perforation was not always found at the level of the colonic tumor. In 11 instances the distended cecum perforated proximal to an obstructing lesion. There were, in addition, six perforations in the bowel just proximal to the tumor, one in an area of acute and chronic colitis, and another at the site of a sigmoid diverticulum. The appendix perforated in two patients, each of whom had a carcinoma of the cecum. The added complication of complete bowel obstruction was found

TABLE 4. *Perforations by Location (118 Cases)*

	Right	Transverse	Left	Total
Free perforation	18(55%)	7(54%)	26(35%)	51(42.5%)
Abscess	10(30%)	4(31%)	37(50%)	51(42.5%)
Fistula	5(15%)	2(15%)	11(15%)	18(15.0%)
Totals	33	13	74	120

TABLE 5. *Primary Operative Procedure in the Management of Perforation*

Operation	Cases	Mortality	5 Year Survival*	For Cure*
Drainage only	3	100%	0%	0%
Fecal diversion only	21	52%	0%	0%
Resections:				
Primary with anastomosis	50	20%	21.9%	9(50%)
Primary without anastomosis	21	24%	10%	2(25%)
Staged procedures:				
1) Cecostomy, resection	2	50%	0%	0%)
2) Colostomy, resection	17	24%	15%	3(23%)
3) Other†	4	25%	50%	1(50%)
Totals	118	29.7%	15.6%	15(35.7%)

* 1958–1967, complete 5 year followup

† 1 ileostomy prior to resection; 3 cecostomy and colostomy prior to resection.

in 27 patients, 22 of whom perforated freely, and the remainder developed abscesses. Eighty-three per cent of the patients with proximal perforation were completely obstructed.

Although the resectability rate for the entire group was surprisingly high (80%), only 52 of the 94 resections (55%) were believed to be curative at the time of surgery. This is in contrast to the overall series of cases of cancer of the colorectum reported by us,[38] in which 83% of resections were done with the intent of cure. In the perforated group, 13 patients were found to have liver metastases at operation. Palliative procedures included the simple placement of drains in three patients, and in an additional 21 individuals a fecal diversion procedure only was performed.

In contrast to our previously reported series, primary resection with or without anastomosis was possible in more than 60% of these cases, and staged resections were performed in an additional 19%. For the right colon, 25 patients (78%) underwent primary resection and anastomosis and only one individual (3%) was subjected to a prior ileo-transverse colostomy. In contrast, in the case of left colon lesions, 31 (42%) individuals were subjected to a primary resection with or without anastomosis, and 22 (30%) underwent resection subsequent to a proximal diverting procedure of some type. Miller wicks or sump drains continued to be used frequently, and were employed in instances of free perforations, abscesses and fistulas in 65%, 67% and 50% of cases respectively. They were used most often in association with diverting procedures (76%), and less frequently following primary resection and anastomosis (52%). It was found that drains were used almost as frequently for right sided lesions as for tumors in the left colon—62% and 67% (Table 5).

TABLE 6. *Incidence of Complications (31 Patients)*

Free perforations	18(35%)
Abscesses	12(24%)
Fistulas	6(30%)
Right colon	6(18%)
Transverse colon	2(15%)
Left colon	28(33%)
Diversion only	9(43%)
Staged procedures	8(35%)
Primary resections	19(27%)

Results

Thirty-six postoperative complications developed in 31 patients. These included wound infection or dehiscence in 13, intra-abdominal abscesses or peritonitis in 7, and pneumonia in 5. As might be expected, these complications of sepsis occurred more commonly after free perforations. They were also associated more often with lesions in the left colon.

Although twice as many total complications were noted following primary resection as after staged procedures, the incidence of complications after primary resection was considerably less. Of interest was the finding that no sepsis in the form of wound infection or intra-abdominal abscess occurred after resections of the transverse colon. In Table 6 is shown the incidence of complications related to the nature of the perforation, the location of the lesion, and type of operative procedure performed. (Table 6).

In this series, 35 patients (29.7%) died during the initial hospitalization. Between 1966 and 1970, however, the overall mortality rate fell to 18.6%. In the group of patients undergoing resection, 27 (64%) of those in whom a palliative procedure only was possible succumbed; and 6 (11.5%) patients died following curative operations. At autopsy, 5 patients operated upon for cure were found to have peritonitis and 2 pneumonia. Mortality rates were highest in patients with free peritonitis. Of the two patients with fistulas that died, one had an associated fecal peritonitis. None of the patients with fistulas who underwent curative resections succumbed. The mortality rate was found to be especially high (43%) when both perforation and obstruction were present. Of these, 21 patients (78%) presented with a free perforation. In this subgroup only 18% of those with perforation of a proximally distended cecum died, compared to 62% of those in whom the perforation was found at the tumor site itself (Table 7).

A complete five year followup is available for all patients through the year 1967. The overall five year salvage of this group of patients was only 15 cases (15.3%). When resections were undertaken for cure, however, the overall five year survival was found to be an encouraging 35.7%. Salvage after curative procedures in all three types of perforation was found to be essentially similar: 33% for free perforation, 35% for abscesses, and 43% for fistulas (Table 8). Of the various curative operations, the sur-

TABLE 7. *Incidence of Mortality After Various Primary Procedures*

Operation	Free Perforation	Abscess	Fistula
Drainage only	1(100%)	2(100%)	0(0%)
Fecal diversion only	8(67%)	2(40%)	2(40%)
Resections:			
Primary with anastomosis	6(38%)	4(17%)	0(0%)
Primary without anastomosis	4(29%)	1(20%)	0(0%)
Staged procedures	2(25%)	4(25%)	0(0%)
Totals	21(41%)	13(25%)	2(11%)

TABLE 8. *Five-Year Survival**

Type of Perforation	Cases
Free perforation	5(33%)
Abscess	7(35%)
Fistula	3(43%)
Total	15(35.7%)

* After resection for cure, 1958–67.

vival rate was highest (50%) after primary resection and anastomosis (Table 5). In this group were 5 patients with left-sided tumors, and 4 with tumors in the right colon.

In the surgical pathology reports available for study, it was found that 92% of these tumors had penetrated to the serosa or beyond, as might be expected, but only 41% revealed lymph node involvement. The overall five year survival of individuals with negative lymph nodes was almost twice as great as when nodes were involved. And, statistically, there was a higher survival rate (20%) when tumor was found to have extended to pericolic fat as compared to serosa only (9.5%). In regard to cell spread, it was found that 60% of the five-year survivors had had drains placed at surgery, and only one patient developed tumor implantation at the site of the drain. In 2 patients left with a colostomy after resection, recurrent tumor developed at the colostomy site (Table 9).

Discussion

Incidence

Carcinomas of the colon and rectum which grow to the point of perforation may present in one of several different clinical patterns; and in any discussion of this complication of cancer, it is, therefore, important to identify the nature of the perforation under consideration. One of the commonest types of "perforation" found in the literature is the adherence of the tumor to one or more adjacent organs. Detailed serial microscopic sections of such adherent areas have revealed that more than 50% of these may be inflammatory, rather than neoplastic, in nature.[2,25,33] Some studies have considered this more favorable type of penetration or perforation,[14,36] while others have reported only cases of free perforation and peritonitis.[24,30] The incidence of free perforation, as found in the literature, varies widely from 0.6% to 4.7%;[6,10,24,25,32] and in our series is 2.5% of cancer of the colon and rectum. Similarly, perforation with abscess formation varies from 0.3% to 4%,[6,7,25,32] and in the present series is again 2.5% Fistulas are less common, and indeed, several series make no mention of them. Up to 1951 only 19 duodenocolic fistulas associated with carcinoma of the colon had been reported.[12] In this study fistulas were found in approximately 1% of cancers of the colon and rectum.

Symptoms and Diagnosis

The continued decrease in time interval between onset of symptoms and operation, found in a survey of all colorectal cancers at the Massachusetts General Hospital between 1937 and 1970,[38] is again demonstrated in the present small series of cases. Glenn and McSherry[9] and Crowder and Cohn[5] report an average duration of symptoms of 4–6 months. This is a somewhat longer interval than was found in our group. In most instances, the onset of acute symptoms of free perforation was preceded by less dramatic complaints. In the case of fistula formation, one might expect a prolonged period of symptoms; but the median duration was found to be similar to that of the abscess group.

The diagnosis of perforated carcinoma of the colon under emergency conditions is not often entertained;[5,13,26,39] and it should be suspected in any acutely ill, elderly patient with prodromal abdominal complaints of a few months duration. The usual patient with free perforation will present with a distended tympanitic abdomen; and the flat and upright abdominal x-ray films may show both free sub-diaphragmatic air and a distended cecum.[29] Less obvious is the acute retro-peritoneal perforation, presenting with subcutaneous or mediastinal emphysema.[26,31] Abscesses usually produce abdominal masses, and cause a change in bowel habits. The patient may not necessarily be febrile. On clinical grounds, abscesses due to carcinoma may be mistaken for perforated diverticulitis.[6,30] In this series of 118 cases, abscesses presented through the inguinal canal in two instances, into the area of the left flank twice, and on one occasion into the upper thigh.

TABLE 9. *Pathological Findings*

Findings	Number of Specimens	5 Year Survival*
Negative nodes	47(59%)	22%
Positive nodes	33(41%)	13%
Depth of Extension:		
To muscularis	6(8%)	25%
To serosa	24(34%)	10%
To pericolic fat	41(58%)	20%

* 1958–1967, complete 5 year followup.

Distribution

Although it is generally accepted that cancer of the colon and rectum have no sex preference, our study resembles that of Thomeret and LeGuillou[35] in that there is a definite predominence of females. The average age was found to be two years older than that of the overall group of cancers; and the peak incidence occurred in the eighth decade, rather than the seventh. There were three times as many patients in the ninth decade of life.[38] The distribution of the tumors in the bowel was identical to that of the obstructing cancers as well as the overall group, with the exception of the rectum, where fewer tumors seem to perforate. Unlike our previous report, where most fistulas were situated in the transverse colon,[7] this type of perforation was evenly distributed in the three major segments of the colon. Perforation and abscess formation, on the other hand, tended to occur more frequently at the sigmoid and recto-sigmoid level. The lower abdominal and pelvic organs provide likely sites for localization of sepsis. In contrast, free perforation with resulting peritonitis predominated in the right and transverse colon segments; and, in addition, cecal perforations proximal to an obstructing cancer were more frequently associated with lesions in these locations than in the left colon.

In our previous series of cases, perforations of the distended colon proximal to the actual site of the cancer were not recorded. Theoretically, there should be less dissemination of tumor cells in such instances. These cases are included here because of the special problems they pose in management. Heschl in 1880 was the first to describe a perforation of the cecum proximal to an obstructing cancer as a "diastatic perforation." Prior to 1936 only 46 cases of diastatic cecal perforation had been reported.[29] A closed segment of right colon, secondary to distal obstruction, is of relatively rare occurrence, as up to 90% ileo-cecal valves are thought to be incompetent.[17,29] However, our finding of 12 such perforations, comprising 24% of the entire group of free perforations, has been noted in other recent reports;[24,30] and suggest that both surgeons and pathologists are becoming increasingly aware of this syndrome.

The importance of recognizing the distended cecum in the presence of distal obstruction has been emphasized by Lowman and Davis.[19] A cecum greater than 9 cm in diameter, as measured on the flat abdominal x-ray is considered by these authors to be in danger of perforation. Since the cecal wall is thin and its diameter greater than that of other segments of the colon, cecal distention in the face of obstruction develops most rapidly, according to the formula $T = (D)X(\pi)X(P)$. In this formula, T represents the tension on the bowel wall, D the diameter of the bowel, and P the intra-enteric pressure. As the cecum distends, the blood supply on the anti-mesenteric border is compromised and a patchy type of gangrene develops.[15,17] We feel that, in instances of carcinoma of the colon which present with obstruction, a cecum of more than 12 cm in diameter must be regarded with concern. In a previous report of 124 cases of obstructing carcinoma of the colon, 15% of cases demonstrated on flat x-ray examination of the abdomen a cecal diameter of over 12 cm.[37]

Treatment and Prognosis

Fistulas. The timing and operative management of perforated colonic cancer varies with the type of perforation. In general, fistulas do not require emergency surgery. Accurate localization of the fistula site can usually be made by means of the barium enema study. Years ago staged operations were preferred. The first of these was a diverting procedure, excluding the fistulous site from the functioning gastro-intestinal tract. In the case of high fistulas, where depletion is marked, primary diversion may be advisable;[4,7] although a short period of intravenous hyperalimentation should be utilized in the hope of improving the status of the debilitated patient so that the preferred treatment by primary resection and anastomosis might be done. Some reports indicate that most malignant fistulas from the colon erode into the stomach and duodenum.[20] In our group of 18 fistulas, the largest number developed between the sigmoid and ileum.

As in the previous series reported from this hospital, this type of perforation provides not only the lowest operative morbidity and mortality, but also the most favorable prognosis. In those individuals surviving resection for cure, the five-year salvage was found to be 43%, compared to a salvage of 50% in the previous series.[7] In our review of all cancers of the colon and rectum in the Massachusetts General Hospital, 54% of patients surviving resection for cure lived five years.[8]

Abscess Formation. In instances of perforation and abscess formation, the initial management must be individualized, and depends on the degree of sepsis present. A palpable abdominal mass may respond to several days of rest in Fowler's position, restriction of oral intake, and antibiotics directed against enteric organisms. In the presence of fever, abdominal pain, and increasing tenderness, early drainage may be necessary as an initial procedure. Although primary resection in the presence of an abscess is hazardous and may be inadequate as a cancer operation, abscesses which are contained, particularly within the bowel mesentery, may often be removed and primary anastomosis performed. The segment of bowel involved is of prime importance. In the right and proximal transverse colon, primary resection and anastomosis is more often possible. In the distal transverse colon and left colon, on the other hand, a staged procedure may often be preferable, and is certainly mandatory when the perforation is accompanied by obstruction. On occasion in a good risk patient, early removal of the cancer may be accomplished by a Hartmann type of procedure in which the cancer, with its lymph node bearing mesentery, may be resected and a colostomy established. At a later date intestinal continuity may be restored.

In the present group of cases of perforation and abscess formation, resections and anastomoses were performed more frequently than were staged procedures. Five patients, however, with associated obstruction, were treated by preliminary diversion. In four of these five patients the tumor lay in the left colon. Some authors[18,21] in discussing the relative mortality of primary resection and staged operations, have noted that the latter method of management carries a mortality four times that of primary resection. The contrast in our data is not as striking, although primary resection, with or without anastomosis, did provide a lower operative mortality (Table 7). It must be remembered that preliminary diversion does not necessarily eliminate the element of infection, and continued drainage from a perforated bowel may result in death due to sepsis. The risks are significant, regardless of the type of management chosen, as an anastomosis of the bowel in the presence of edema is fraught with hazards. This is particularly so in lesions of the left colon. We have become convinced, however, that "it is the disease and not the operation that most often causes death, and more attention should be paid to the eradication of the disease."[7] In the present review of cases of perforation and abscess formation, a five-year cure rate of 35% in those individuals operated upon for cure, compares favorably with the 33% survival noted in our previous report.

Free Perforation with Peritonitis. Cancers which perforate freely into the peritoneal cavity present true surgical emergencies. Whether the peritonitis is localized or widespread, immediate steps must be taken to combat the shock or impending shock of peritonitis. A central venous catheter must be placed, intravascular volume restored, and broad spectrum antibiotics administered parenterally in preparation for abdominal exploration. Only a few decades ago, virtually all of these patients succumbed, whether or not laparotomy was undertaken; and, today, the mortality is as much as four times that found in the fistula group of patients. As noted in our earlier study, resection of the tumor results in a lower mortality than that following lesser procedures; and the present review reveals a gratifying increase in resection rate from 5% to 59% of cases. Several other reports have recommended primary resection, with or without anastomosis, when the tumor itself perforates freely into the peritoneal cavity.[7,10,21,22,24,30] We fully agree with this method of management, although statistically our mortality is slightly lower after the resection is done in stages.

The location of the tumor appears to have little bearing on the operative mortality, as 48% of patients with free perforation of the right colon died, and 51% of those with lesions on the left side succumbed. In the right colon, only 1 patient undergoing a staged resection died, and the other deaths followed primary resection. Death after resection of a left sided lesion occurred in 2 patients undergoing staged procedures, and in 5 individuals who had primary resection without anastomosis. It is obvious that the operative mortality is high following any type of procedure for the freely perforated cancer, and in this respect compares with the mortality of tumors associated with both obstruction and perforation. The fact that the overall mortality for perforated cancer of the colon is found to be greater than that reported in our earlier study (30% as against 23%) is in part due to the fact that there were twice as many free perforations in the present series of cases.

Mortality following diastatic cecal perforation is even greater and has been reported as high as 90%.[1,5,10,17] Russell[30] in his report has indicated that when the tumor itself has perforated, a "lighter contamination" occurs. In our series, however, only 2 patients with diastatic cecal perforation died (18%), 2 (or 33%) succumbed when the perforation occurred just proximal to the tumor, and 17 (or 50%) died when the site of perforation lay at the tumor level itself.

The preferred treatment of diastatic perforation of the cecum, when the cancer is in the right colon, is primary resection. One of 4 patients so treated succumbed. Both individuals with lesions in the transverse colon, similarly treated, survived. In the case of a cecal perforation with the primary cancer in the left colon, plication of the cecum,[24] cecostomy,[28] and sub-total colectomy[11] have been described in the literature. In our group, 3 individuals underwent cecostomy and transverse colostomy

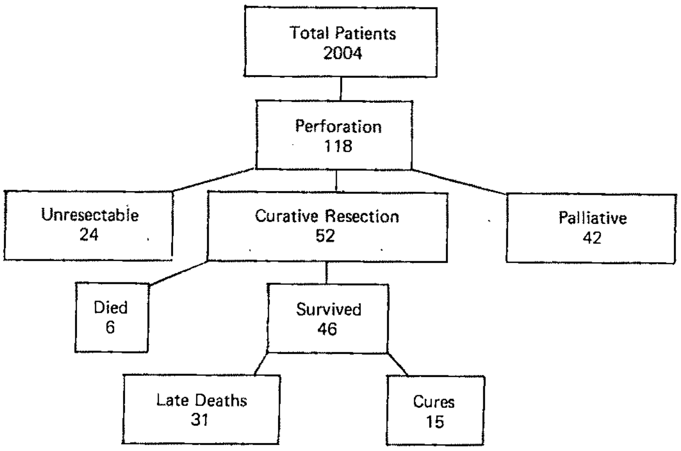

FIG. 1. MGH 1958–70. Carcinoma of the colon with perforation.

prior to resection of the primary tumor, 1 patient was subjected to a subtotal colectomy and anastomosis, and 1 underwent a staged procedure consisting of ileostomy for a gangrenous cecum, followed by a resection of the primary tumor of the sigmoid. Only 1 of these individuals died.

In a previous report from this hospital, only 1 of 9 patients with a free perforation (11%) survived five years. In the past 15 years, 5 of 51 patients with this type of unfavorable perforation were found alive after five years. And if the survival rate is adjusted for those individuals who had survived curative resection, 42% survived five years. Again, this compares favorably with the overall five year survival rate for all cancers resected for cure of 54% reported previously. As suggested by Liechty *et al.*,[18] it is likely that free cancer cells are nonviable at the time of bowel rupture, and are incapable of implanting themselves successfully on an inflamed peritoneum (Fig. 1).

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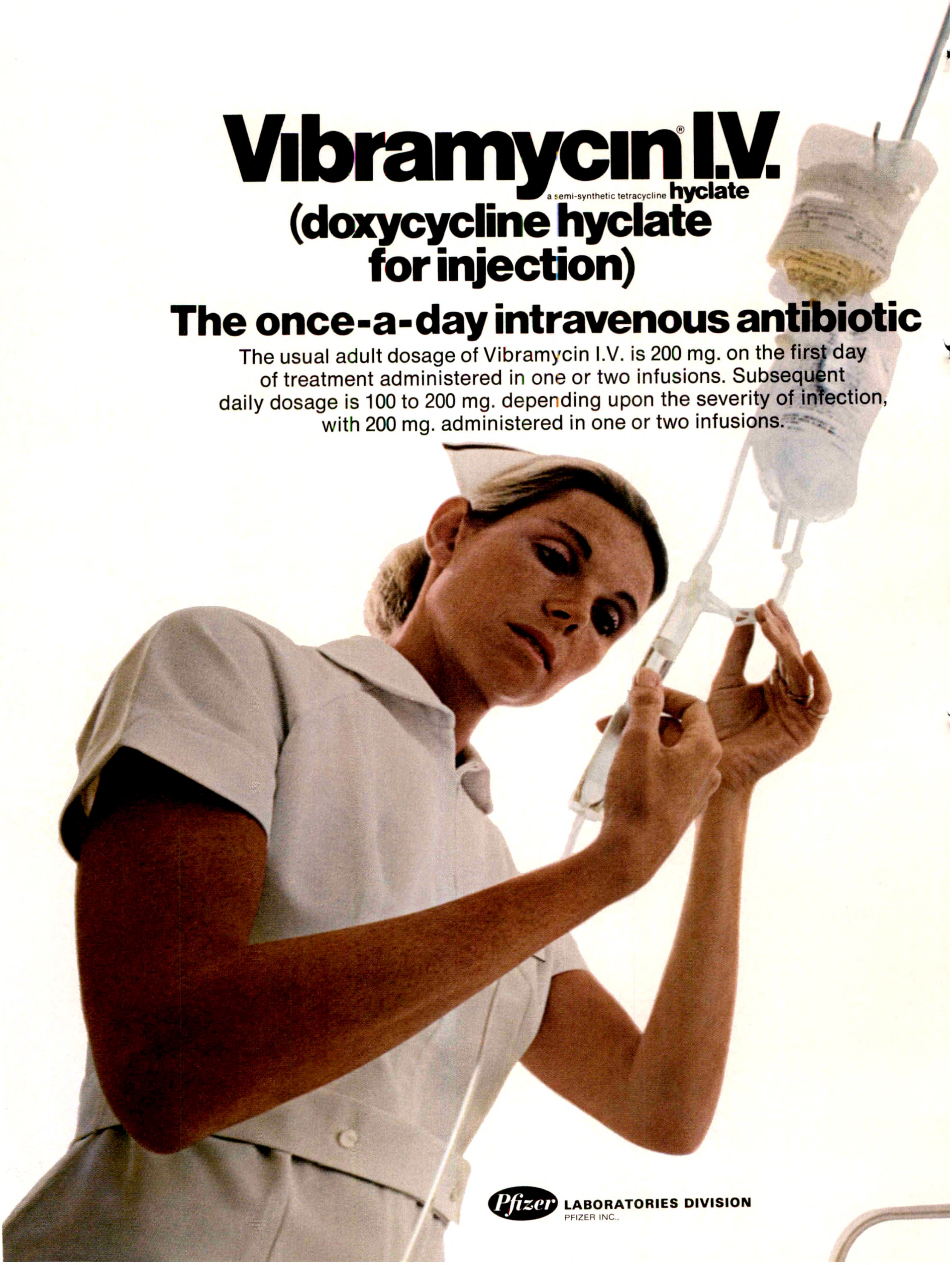

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The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

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The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

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A semi-synthetic tetracycline

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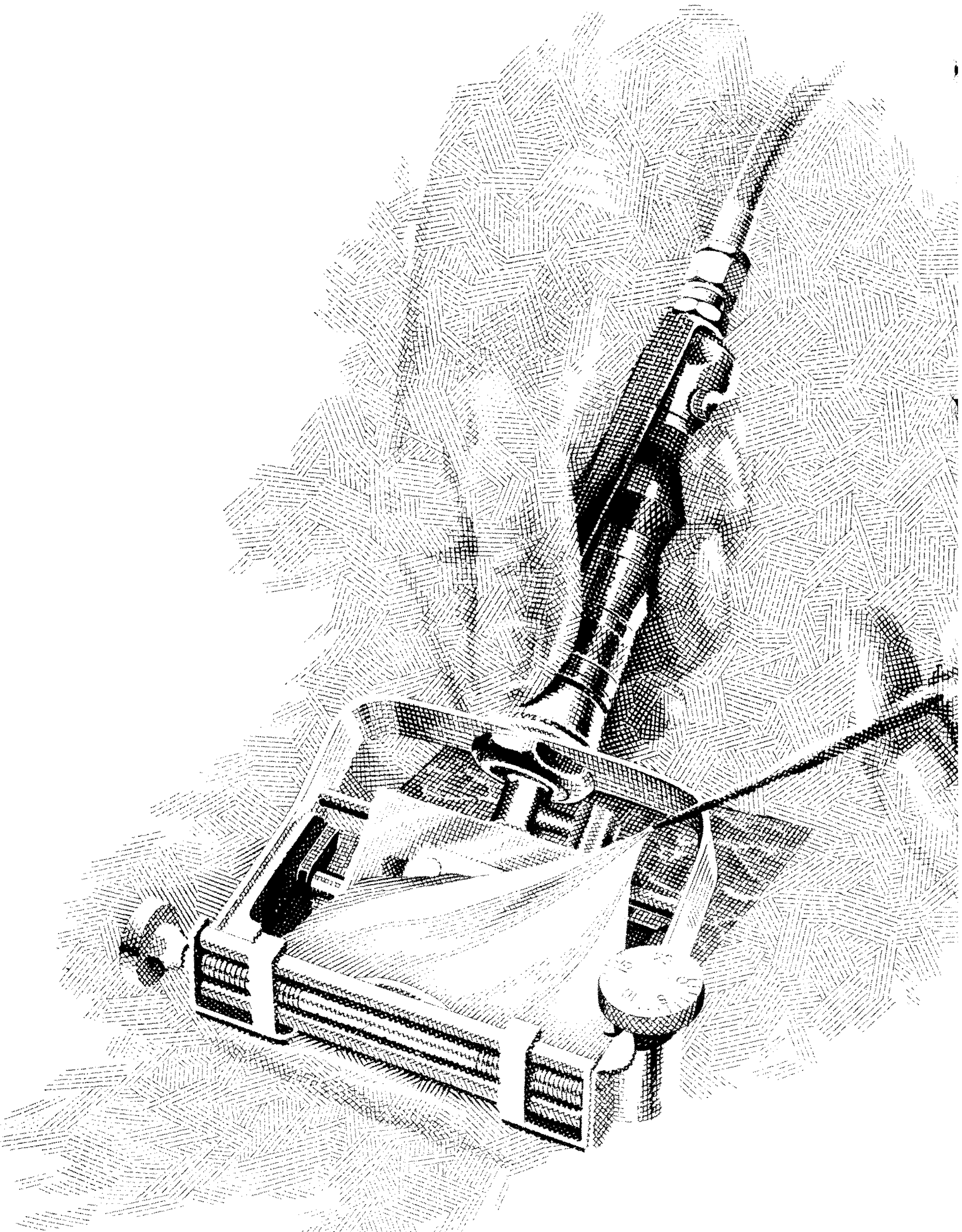

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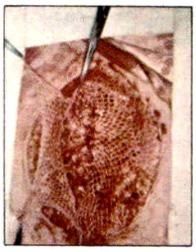

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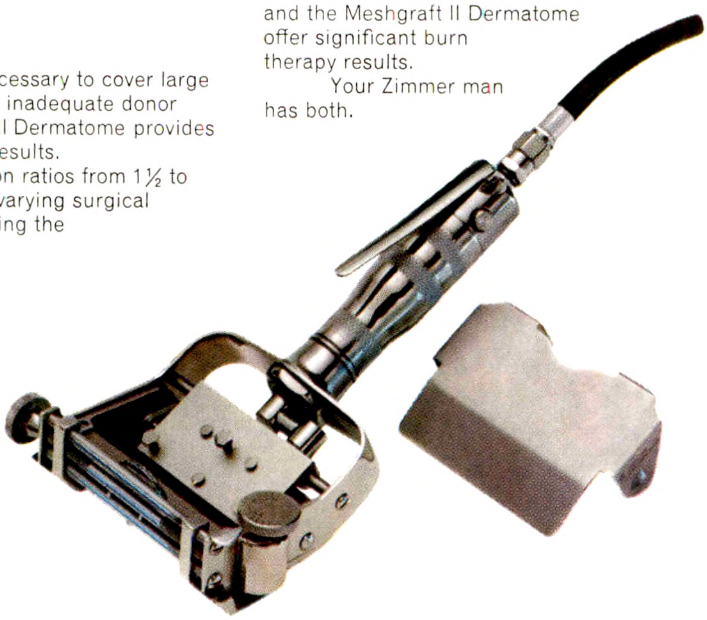

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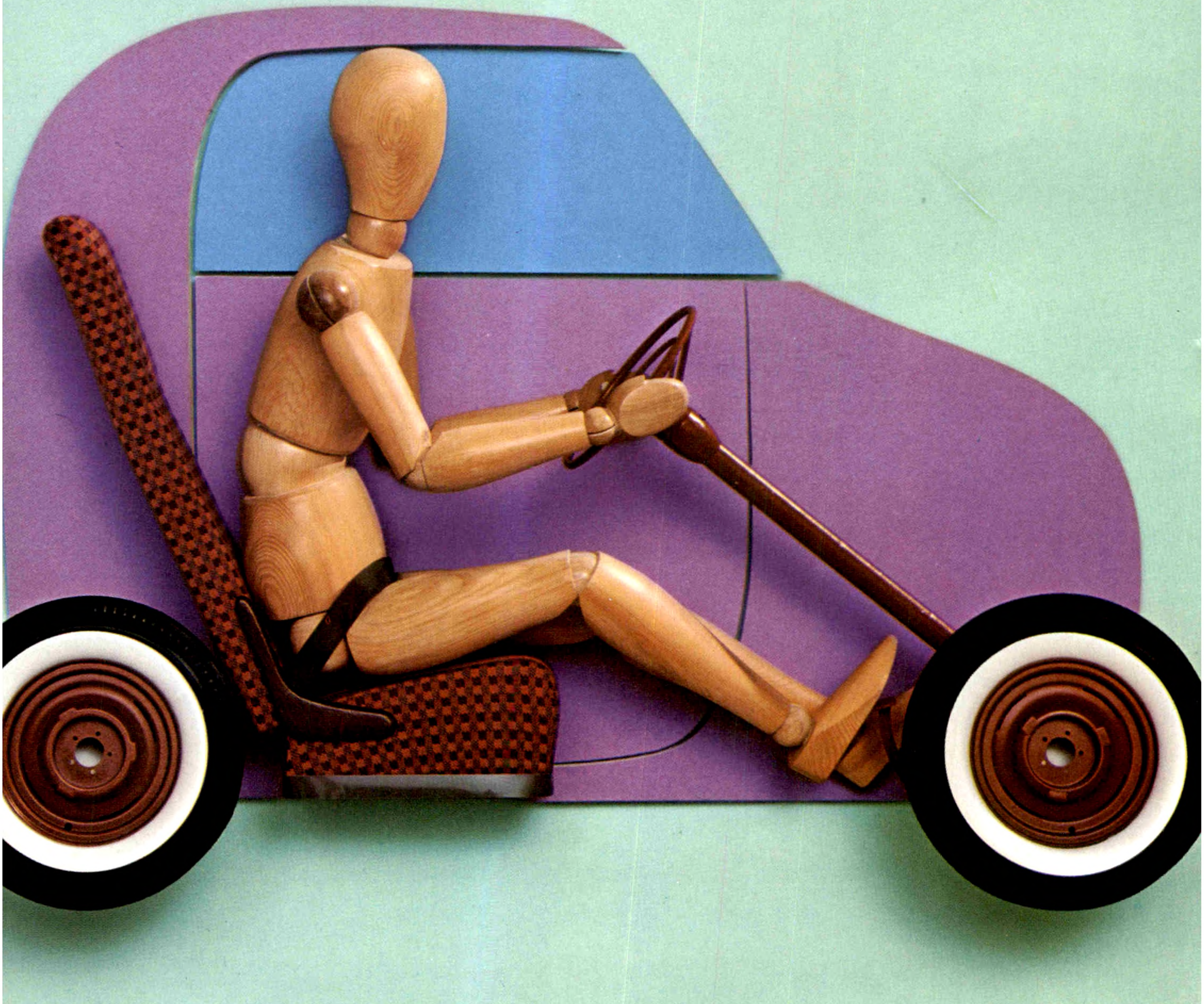

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Precautions:
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It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

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Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

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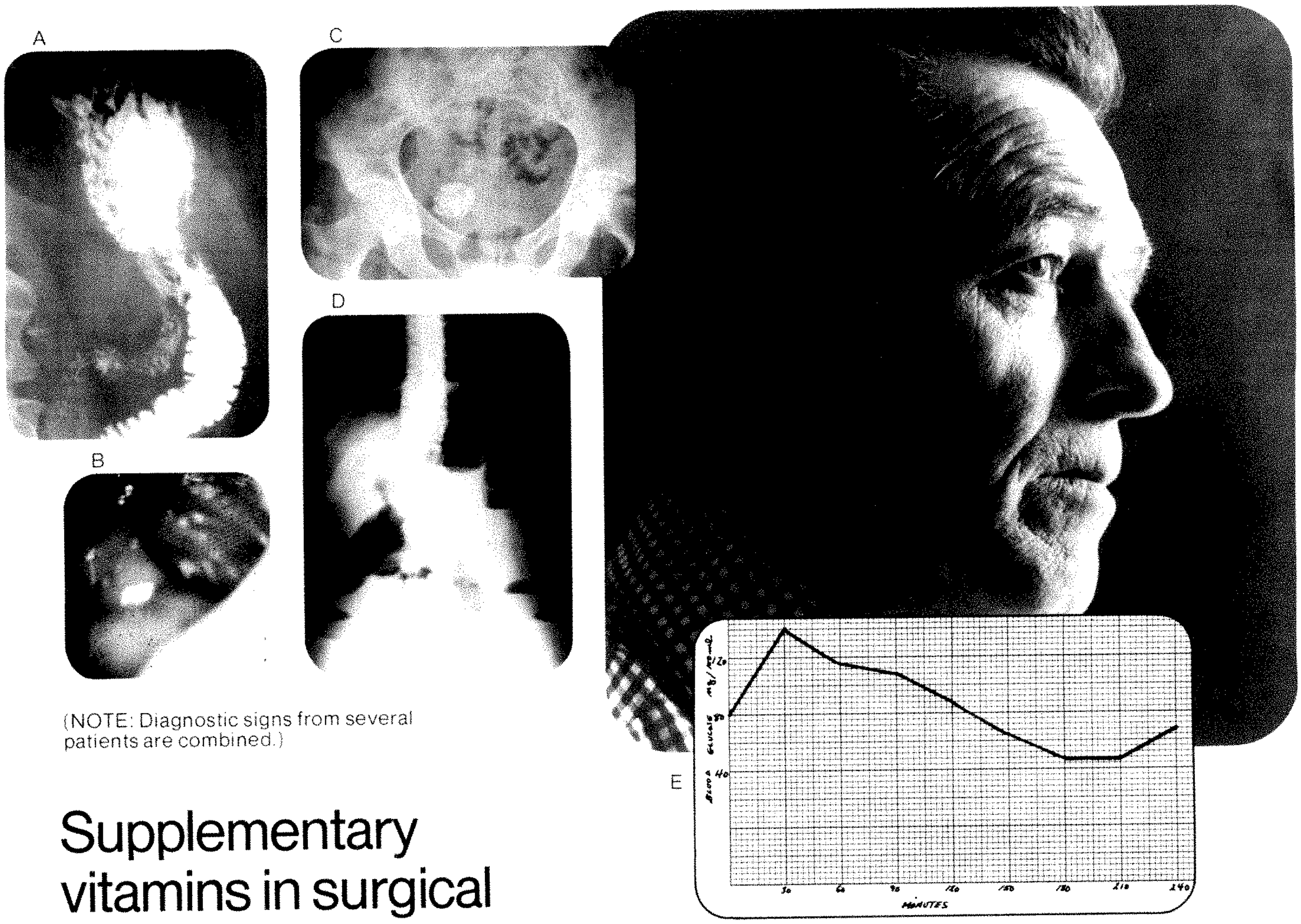

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See next page for summary of Product Information.

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Calcium pantothenate	20 mg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Folic acid	0.5 mg
Ascorbic acid (Vitamin C)	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.

Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.

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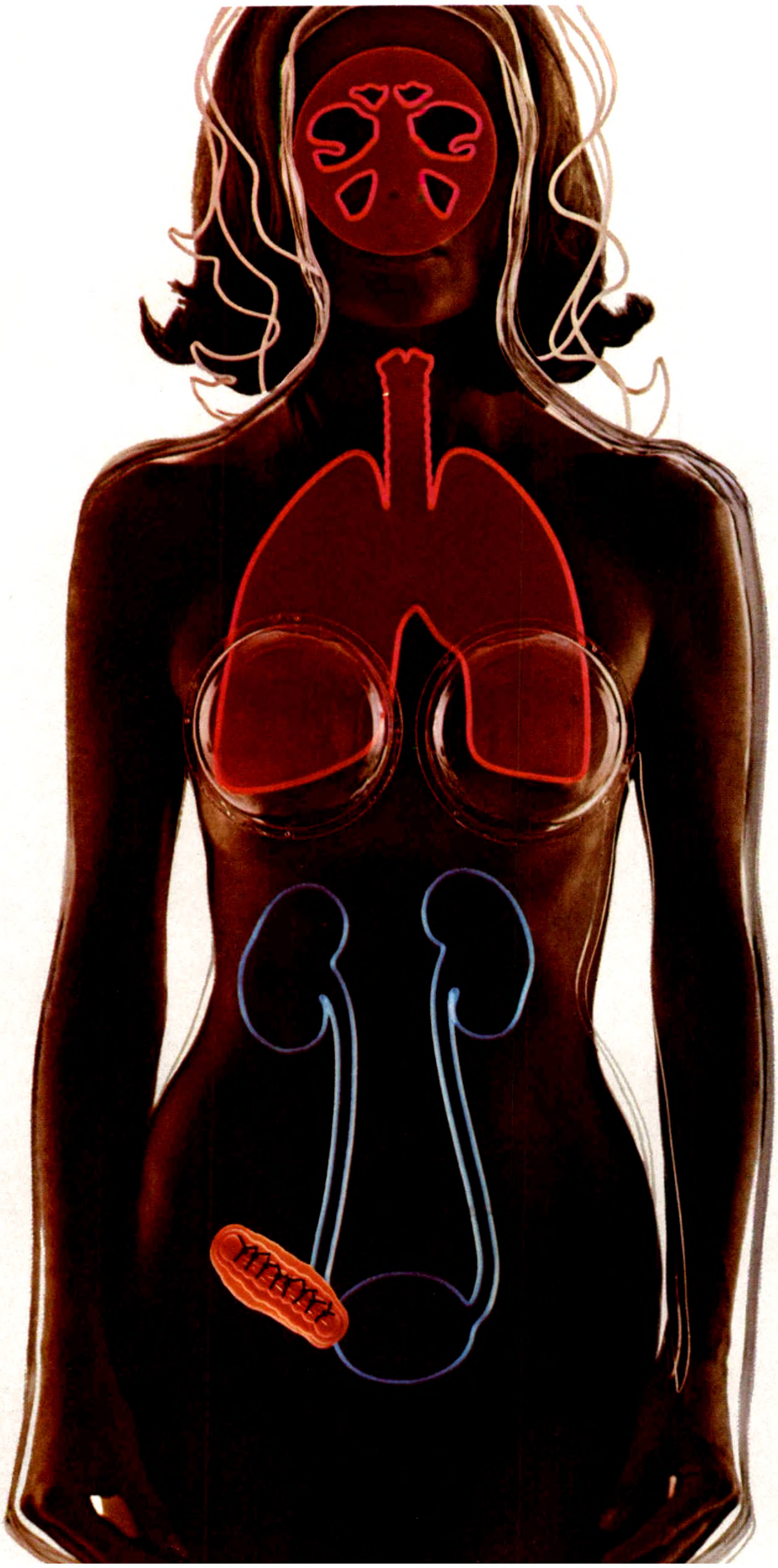

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Respiratory tract infections caused by group A beta-hemolytic streptococci and *D. pneumoniae.*

Urinary tract infections caused by *E. coli, Pr. mirabilis,* and *Klebsiella* species.

Skin and soft-tissue infections caused by staphylococci.

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae, H. influenzae* and staphylococci.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

- **Documented safety.**
- **Rapidly absorbed. Average peak serum levels within 1 hour.**

(Approximately 9 and 16.5 mcg./ml. at 1 hour with 250 and 500 mg. capsules, respectively, in normal adult volunteers.)

- **High urinary levels.**

(Peak concentration of approximately 3200 mcg./ml. with 500 mg. capsule dose in normal adult volunteers.)

- **Excreted essentially unchanged in the urine.**
- **Acid stable. Can be given without regard to meals.**

'Anspor' is contraindicated in patients with known hypersensitivity to the cephalosporins. **In penicillin-sensitive patients, cephalosporin C derivatives should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.**

Adverse Reactions

The following adverse reactions have been reported: glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn; mild urticaria or skin rash, pruritus, joint pains; transient eosinophilia, leukopenia, neutropenia; transient rise of SGOT, SGPT, total bilirubin, BUN; dizziness, tightness in the chest, and candidal vaginitis.

For a brief summary of prescribing information, including indications, contraindications, warnings, precautions, adverse reactions, and dosage, please see the following page.

New from SK&F

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CEPHRADINE

capsules: 250 and 500 mg.
for oral suspension: 125 and 250 mg./5 ml.

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

DESCRIPTION

Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephradine is active against the following organisms *in vitro*:

- Beta-hemolytic streptococci
- Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
- *Diplococcus pneumoniae*
- *Escherichia coli*
- *Proteus mirabilis*
- *Klebsiella* sp.
- *Hemophilus influenzae*

Note—Some strains of enterococci (*Streptococcus faecalis*) are resistant to cephradine. It is not active against most strains of *Enterobacter* sp., *Pr. morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephradine and methicillin-type antibiotics.

INDICATIONS

Anspor (cephradine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated micro-organisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae*.

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*, *Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Anspor (cephradine, SK&F) is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephradine is secreted in breast milk during lactation.

PRECAUTIONS

Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy as cephradine accumulates in the serum and tissues. See *DOSAGE AND ADMINISTRATION* section for information on treatment of patients with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of non-susceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephradine therapy, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pruritus, and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the chest and candidal vaginitis.

DOSAGE AND ADMINISTRATION

Anspor (cephradine, SK&F) may be given without regard to meals.

Adults: For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally spaced doses. For acute infections of the urinary tract, including prostatitis, and pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equally divided and spaced doses. For otitis media due to *H. influenzae*, doses from 75 to 100 mg./kg./day in equally divided and spaced doses are recommended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram, q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule is necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance dose is 500 mg. at following time intervals: creatinine clearance >20 ml./min., 6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-24 hours between doses; creatinine clearance 10-14 ml./min., 24-40 hours between doses; creatinine clearance 5-9 ml./min., 40-50 hours between doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

HOW SUPPLIED

ANSPOR (cephradine, SK&F) Capsules—250 and 500 mg.

'ANSPOR' for Oral Suspension—Pleasant fruit-flavored oral suspension which, after reconstitution, provides 125 mg. or 250 mg. of cephradine per 5 ml. teaspoonful.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa. 19101

A New Oral Antibiotic

Fungal Septicemia in Surgical Patients

ROBERTO J. RODRIGUES, M.D.,[*] WILLIAM I. WOLFF, M.D., F.A.C.S.[†]

From Beth Israel Medical Center, New York, New York

Opportunistic systemic fungal infections are more frequent than generally realized. Increased awareness and a high index of suspicion of fungal super-infection in the presence of sepsis is required to bring about recognition and therapy. The intravenous catheter is an important portal of entry or may act as a foreign body favoring localization of a septic process. In its presence, fungemia must be guarded against. Whenever an intravenous catheter is removed, its tip should be cultured. Removal alone may be a critical item in therapy. In febrile patients, in whom the course of fever is not established, frequent blood cultures with attention directed specifically at fungi should be obtained. Fungi are not easily isolated and identified and only by requesting special attention from the microbiologist can the diagnosis be established in the average institutional laboratory in time to permit appropriate therapy. Since available therapeutic measures are strikingly effective when instituted early, awareness and alertness on the part of the clinician constitute the key to cure.

A MAJOR PROBLEM in many hospitals today is infection acquired in the hospital itself (nosocomial infections). The normal biologic state of man is not germ-free, but rather a balance between the host and a wide variety of organisms. Infection may be regarded as a quantitative disturbance of this normal balance resulting from a lowering of host resistance or by overwhelming invasion by endogenously or exogenously derived organisms. While hospitalization itself does not predispose the patient to infection, because of either his disease or his therapy he is an "altered host" with attendant changes in his cellular and humoral defense mechanisms. Moreover, the processes involved in diagnosis and treatment frequently compromise the integrity of the physical barriers against infection.

The pattern of infection and the etiologic agents responsible for nosocomial infections change with time and place; the much feared *Staphylococcus aureus* of the late forties and fifties gave way in the early sixties to the emergence of gram-negative infections.[3,4,29,34,48,49,82] During the last few years, a striking increase in the incidence of clinically significant and sometimes fatal systemic fungal disease in hospitalized patients has been reported.[10,21,25,26,49,56,91,96] Many of those hospital-acquired infections are caused by saprophytic fungi which are consistently present in the environment. Under special circumstances they may produce infections best described as "opportunistic."[59,93] When those fungi become disseminated throughout the blood stream the mortality is high.[21,33,38,49,54,91] Our experience with this type of infection is the basis for this report.

Data

Thirty patients had fungal septicemia with positive blood cultures between January, 1969 and June, 1973. Records were reviewed and the culture evidence evaluated in terms of clinical findings. Associated infections and documentation of the presence of fungi at various sites were critically evaluated according to criteria established by previous authors.[10,26] Patients with bacterial sepsis were excluded. Attention was directed to age, clinical diagnosis, indwelling catheters, radiation, parenteral hyperalimentation, antibiotic therapy, steroids and other drugs (Table 1).

Debilitating disease, old age and visceral failure were common. All patients with fungal septicemia were receiving one or more broad-spectrum antibiotics and all but three had an intravenous catheter at the time of occurrence of fungemia. In 23 patients (76.6%) culture

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Submitted for publication December 26, 1973.

[*] Fellow in Surgery, Beth Israel Medical Center, Instructor in Surgery, Mount Sinai School of Medicine, CUNY, New York.

[†] Director of Surgery, Beth Israel Medical Center, Professor of Clinical Surgery, Mount Sinai School of Medicine, CUNY, New York.

Reprint requests: Roberto J. Rodrigues, M.D., Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, New York 10003.

TABLE 1. *Cases of Fungal Septicemia: January 1969–June 1973*

Patient	Age/Sex	Underlying Disease	Source	Etiologic Agent	Course
1. N. P.	58 f	Adeno Ca of cardia Esophagogastrectomy Mediastinitis	Subclavian catheter Hyperalimentation	*Candida tropicalis*	Septic shock Expired
2. M. G.	67 f	Pyelonephritis, ASHD Renal failure Fungal peritonitis	Peritoneal dialysis catheter	*Candida albicans* *Candida tropicalis*	Septic shock Expired
3. W. L.	63 m	AdenoCa pancreas Diabetes mellitus Pneumonia, Cirrhosis	Peripheral IV catheter	*Candida tropicalis*	Fever, chills Survived
4. F. L.	77 m	Ca lung, SVC syndrome Radiation	Subclavian catheter Hyperalimentation	*Candida albicans*	Septic shock Expired
5. L. R.	95 m	BPH, Hematuria	Peripheral IV catheter	*Candida albicans*	Fever Survived
6. F. G.	70 m	Ca lung, Diabetes Peripheral Vasc. Dis.	IV catheter Urinary bladder?	*Candida albicans*	Septic shock Expired
7. R. E.	65 m	Ca esophagus T-E fistula	Subclavian catheter Hyperalimentation	*Candida albicans*	Septic shock Expired
8. G. F.	73 f	Ca esophagus, Radiation Mediastinitis	Peripheral IV catheter	*Candida albicans*	Fever, shock Expired
9. T. F.	32 m	Fungal pneumonia Heroin addiction	Lungs	*Candida tropicalis*	Fever Survived
10. A. J.	45 f	Regional enteritis Malabsorption	Subclavian catheter Hyperalimentation	*Candida sp.*	Fever, shock Survived
11. L. S.	61 m	Esophageal stricture Esophagogastrectomy	Peripheral IV catheter	*Candida albicans*	Fever, chills Shock, expired
12. J. S.	64 f	Duodenal fistula Renal Ca, Radiation	Cutdown Hyperalimentation	*Torulopsis glabrata*	Fever, shock Expired
13. S. W.	73 f	Miocardial infarct Fungal pneumonia	Peripheral IV catheter	*Candida tropicalis*	Fever, shock Expired
14. E. A.	32 f	Chronic Renal failure	Peripheral IV catheter	*Candida albicans*	Septic shock Expired
15. M. R.	9 m	Regional enterocolitis	IV catheter, wound	*Candida tropicalis*	Fever, survived
16. D. F.	25 f	Ruptured AP, pelvic abscess, fecal fistula	Peripheral IV catheter	*Candida albicans* *Rhodotorula sp.*	Fever, shock Survived
17. M. E.	59 f	Hepatic cirrhosis, GI bleeding, Pneumonia	Peripheral IV catheter	*Candida tropicalis*	Fever, shock Expired
18. Y. R.	69 f	Vaginal hysterectomy Diabetes mellitus	Peripheral IV catheter	*Candida albicans*	Fever, chills Survived
19. M. D.	68 m	Bleeding DU, ASHD Pacemaker insertion	Peripheral IV catheter?	*Candida sp.*	Fever, survived
20. L. B.	65 f	Decerebrate coma	Peripheral IV catheter?	*Candida tropicalis*	Fever, shock Expired
21. R. Z.	78 f	Massive small bowel infarct	Subclavian catheter	*Candida albicans*	Fever, shock Expired
22. A. S.	75 m	Subarachnoid hemorrhage, Steroid	Peripheral IV catheter	*Candida albicans*	Septic shock Expired
23. S. C.	68 f	Fract. pelvis, Fat embolism, Diabetes	Undetermined	*Candida tropicalis*	Fever, shock Expired
24. G. F.	72 f	Ca esophagus, Radiation Steroid	Subclavian catheter Hyperalimentation	*Torulopsis glabrata*	Fever, shock Survived
25. M. D.	43 f	Portal hypertension Biliary cirrhosis	Subclavian catheter Hyperalimentation	*Candida albicans*	Septic shock Expired
26. J. V.	56 m	R hepatic lobectomy Stab wound of liver	Peripheral IV catheter?	*Candida stellatoidea*	Fever, chills Survived
27. J. R.	30 m	Gunshot wounds, Heart laceration, splenectomy, R nephrectomy, Liver lac.	L subphrenic abcess	*Candida albicans*	Fever, shock Survived
28. T. N.	29 m	Colovesical fistula Choledocolythiasis Heroin addiction	GI tract?	*Candida albicans*	Fever, shock Survived
29. L. Y.	65 m	Perf. sigmoid divert. Fecal peritonitis Wound disruption	Subclavian catheter Hyperalimentation	*Candida albicans*	Fever, shock Expired
30. M. S.	62 m	Multiple trauma Splenectomy, tracheostomy Shock lung	Peripheral IV catheter	*Candida albicans*	Fever, survived

of the catheter tip yielded the same organism found in blood cultures. Eight patients were receiving parenteral hyperalimentation. The portal of entry was unclear in five cases but in three, suspicion could be cast upon an intravenous catheter.

Candida albicans was found to be the most frequent pathogen recovered (56.6% of cultures). Other species of Candida were also encountered. Rare fungi (Torulopsis and Rhodotorula) were identified in three patients (Table 2).

TABLE 2. *Isolates from 30 Patients with Fungal Septicemia*

Candida albicans	17
Candida tropicalis	9
Candida stellatoidea	1
Candida sp.	2
Torulopsis glabrata	2
Rhodotorula sp.	1
	32*

* Mixed fungal infection in 2 cases.

Clinical Picture

All patients presented with a constellation of high fever (39.5–40.5 C), hypotension, diaphoresis and rigors. As most clinicians are now alerted to the obvious similarities between these symptoms and the mainifestations of septicemia by gram-negative bacteria, most of the patients were treated with this presumptive diagnosis. They received intravenous antibiotics, steroids and balanced electrolyte solution. Only four cases received specific antifungal therapy (Amphotericin B) and in this small group there were three survivors. Amphotericin B was administered by slow intravenous infusion prepared according to the manufacturer's specifications. Initially, 0.25 mg/kg was infused daily. This dosage was gradually increased to 0.75 mg/kg with close monitoring of renal, hepatic and hematopoietic functions. The longest duration of therapy was four weeks. No complications were observed in our patients. Overall mortality was 56.6% (17/30). In many patients the diagnosis of fungemia was only arrived at upon post mortem because the results of fungi in blood cultures were either overlooked or considered as contaminants. In a few instances, the results were reported by the laboratory as a terminal event or after the patient had expired.

Discussion

Saprophytic fungi are ubiquitous in nature.[23,24,91] Until very recently considered nonpathogenic, their latent potential to become invasive and produce serious infection has been well documented.[2,10,21,25,26,30,33,38,40,42,44,45,47,49,56,60,81,91,93] Usually these infections are caused by the common inhabitants of the skin and mucous membranes, such as Candida and a few other species.[7,53,70] However, in recent years less common organisms are emerging as the responsible agents.[27,38,40,44,49,54,56,60,63,81,88]

Experimental studies indicate that physiologic alteration in the host predisposes the establishment of such infections.[40,42,43,45,58] The natural virulence of most fungi is low, so that metabolic disturbances in the host are likely predisposing factors in the development of systemic fungal infections.[10,33,49,55,89,91,93] Other factors involved are extreme youth or age, debilitation and malnutrition;[13,91,98] consumptive diseases, particularly cancer[33,47,49,55,92] and leukemia;[12,38,47,78] diabetes mellitus;[7,49,70] renal failure;[35,46] open heart surgery;[27,50,53,71,73] transplantation;[80] trauma;[22,33,67,98] colonic sterilization;[18] oral contraceptives;[83] drug addiction;[41] treatment with broad-spectrum antibiotics;[21,33,49,62,87] pharmacologic doses of steriods;[30,32,49] immunosuppressive drugs;[30,38,80] prolonged infusions via intravenous catheters[9,16,21,49,52,65,68,74,90,97] and intravenous hyperalimentation.[6,13,19,49,81,85]

Bizarre clinical pictures may occur when the fungi create localized microabscesses in the central nervous system,[11,21] bones,[1,41] esophagus,[36] urinary tract,[72,86] internal genitalia,[31,76] and peritoneum.[46,51,64]

Unfortunately, the manifestations are so protean and the fungal infection so obscure that early diagnosis is unusual unless the clinician is alert to this possibility.[10,21,26,49,60,93] Initial blood cultures may fail to yield the organism,[2,49,91] or such isolates may be obtained too late for effective institution of therapy.[10,21,26,38] Positive blood cultures alone are not pathognomonic and may only represent transient contamination of the blood stream. The diagnosis must depend on a combination of clinical and laboratory findings and careful consideration of the multiplicity of factors comprising the clinical setting. The presence of fungi in cultures taken from multiple sites plus persistent fever of the septic type, a leukemoid reaction in the peripheral blood and presence of budding fungi in the urine can be considered strong evidence for the diagnosis of disseminated fungal infection.[10,26] There is experimental evidence that the fungi may be viable in tissues, such as the kidneys and lungs, and may produce recurrent episodes of fungemia with completely symptom free intervals. Serum agglutination and precipitin reactions against a cell-free cytoplasmic sonicate of *C. albicans* have been shown to be the best diagnostic tools if suspicions are aroused.[78,91] In a few instances hyphae can be found in the peripheral blood.[77] Spontaneous remission of the infection merely by removal of the source, usually an intravenous catheter, has been described[21] and probably happens quite frequently.

Potent fungal toxins have been isolated[15,66,84] and in the severe forms of the infection with fungemia, a shock state may develop which is strikingly similar in its clinical presentation to gram-negative sepsis; this makes diagnosis and proper treatment difficult.[21,25,33,49,54,63,81] Disseminated intravascular coagulation characterized by thrombocytopenia, increased prothrombin time and partial thromboplastin time, presence of fibrin split products in plasma and glomerular intravascular fibrin thrombi[17] has been found in association with fungemias[20,75,79] and the presence of a plasmacoagulase in fungi has been reported.[90]

Treatment

Specific antifungal therapy should not be used in every patient with positive blood cultures. In those patients with clinical evidence of systemic infection the recommended treatment is Amphotericin B starting with a low dose and progressively increasing to a daily dose of 1 mg/kg given over a six-hour period.[5,33,37,49,57,59,96] Usually two weeks of therapy eradicates the infection. Lower dosages have been used with effective clinical response and the duration of therapy appears to be more important than the total dosage received. The toxic effects are many and serious, and are described elsewhere.[37]

Two new drugs have recently been clinically tested: 5-fluorocytosine[5,28,39,61,94,95] and clotrimazole.[8,61,69] The first appears to be the more promising. It has been used orally in daily doses of 150 mg/kg or more. The attractive aspects of 5-fluorocytosine are its lack of toxicity in comparison with Amphotericin B, its rapid renal clearance and high tissue levels.[94] However, leukopenia, anemia and elevated serum liver enzymes have been reported with its use.[39]

The biweekly prophylactic instillation of small doses of Amphotericin B into intravenous catheters placed for prolonged periods appears to prevent effectively Candida overgrowth.[14]

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Long Term Pulmonary Artery Pressure Monitoring in the Management of the Critically Ill

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Detailed experience during prolonged pulmonary artery pressure monitoring (up to 19 days) in 86 seriously ill patients is reviewed. Strict adherence to a protocol developed for insertion and maintenance of Swan-Ganz catheters resulted in successful catheterization of the pulmonary artery in nearly 100% of patients with minimal morbidity. Several technical problems associated with the use of this catheter-monitoring system are described, excessive balloon inflation with resultant misleading, spuriously high pressure measurement being one of the most serious. Most technical problems are avoidable. In the majority of critically ill patients both central venous and pulmonary artery diastolic pressures proved to be inaccurate estimates of pulmonary artery wedge pressure (PAW). PAW was a useful adjunct in the assessment of intravascular volume and hemodynamic alterations in these patients. The Swan-Ganz catheter serves for other functions including collection of mixed venous blood for cardiac output determination and injection of contrast material for small vessel angiography. Measurement of pulmonary artery wedge pressures should be routinely included in the sequential hemodynamic evaluation of most patients sufficiently ill to be hospitalized in an intensive care unit.

ALTHOUGH central venous pressure monitoring provides useful information in the management of the acutely ill patient,[1,4] there has been a need for clinical assessment of pressures in the pulmonary artery and left side of the heart. However, there was no practical method to obtain such pressures at the bedside until 1970 when Swan and colleagues[8] described the use of a flow-directed, balloon-tip catheter which could be passed blindly from a peripheral vein into the pulmonary artery in humans. The inflatable balloon on this catheter not only facilitated passage into the pulmonary artery, but when inflated to obstruct flow afforded measurement of pulmonary artery "wedge" pressure, a close approximation of left atrial pressure. During a 10-month period beginning in August 1971, pulmonary artery pressure monitoring with the Swan-Ganz balloon catheter was carried out in approximately 200 patients, representing some 20,000 patient-hours' experience. The data in this report are based on a chart analysis of 86 randomly selected patients who underwent long-term pressure monitoring.

Patients

In distinction to other reports of the clinical use of pulmonary artery and pulmonary artery wedge pressure monitoring,[3,6,7] we have focused attention here on patients with a wide spectrum of critical illness seen predominantly in the intensive care unit. The ages of the 86 patients ranged from 9 to 94 years. The average duration of continuous pulmonary artery pressure monitoring was 89 hours and varied from a few hours to 19 days.

All patients were considered to be critically ill; 71 patients (83%) were hospitalized in an intensive care unit, and 15 patients (17%) in a coronary care unit. Commonly encountered problems included clinical shock associated with bacteremia, hypovolemia, or cardiac pump failure; pulmonary edema due to heart failure, shock lung syndrome or central nervous system trauma; acute respiratory failure; acute renal failure; drug overdose; and post-cardiac resuscitation state. The patients underwent pulmonary artery catheterization to: 1) assess intravascular volume and cardiac status and/or; 2) monitor those with suspected cardiac or pulmonary disease during volume replacement; and/or 3) provide for sequential hemodynamic evaluation in the management of clinical

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shock. In approximately 20% of the patients studied in the intensive care unit, the catheters were inserted within one hour of admission. However, the average delay after the recognized or suspected onset of a hemodynamic problem was nearly 16 hours.

An average of 51 sets of measurements were obtained in each of the 86 patients (pulmonary artery systolic, mean, diastolic, and mean wedge pressures represent one set). Pulmonary artery pressures were displayed continuously, and data were recorded, on the average, every 1.8 hours. However, as many as 12 wedge pressures were recorded during a single hour.

Techniques

Pulmonary artery and wedge pressures were monitored on either a Statham P23Db transducer attached to the catheter via a short length of tubing or a Microdot MS-10 transducer coupled to the 5F balloon catheter (Edwards Laboratories, Santa Ana, California). Central venous pressures were measured with standard water manometers using zero reference points identical to that for the pulmonary artery pressure measurements. A strict protocol for catheter insertion was followed:

1. Under sterile conditions, a cutdown is performed over the median basilic vein in the antecubital fossa. Since the catheter may be left in place for a number of days, it is important that a careful surgical prep is performed and that the entire procedure is done under aseptic conditions. Daily dressing change and topical antibiotic application is routinely done.

2. Prior to insertion, the balloon tip of the catheter is inflated under sterile water with 0.8 cc air to determine if there are leaks or obstructions with inflation or deflation. (In our experience, approximately 5% of the *new* catheters were defective.)

3. A venotomy is performed and the catheter tip carefully inserted into the vein. The possibility of balloon damage is decreased by avoiding the use of instruments when the catheter tip is introduced.

4. The fluid-filled catheter is inserted an average distance of 45 cm. The balloon is then inflated with 0.8 cc air and the catheter slowly advanced under pressure monitoring control to the right ventricle. After measuring right ventricular pressure, the catheter is slowly advanced into the pulmonary artery until a wedge pressure tracing is noted. If the pulmonary artery is not entered within 15 cm after passing the tricuspid valve, the catheter is likely coiled in the right ventricle; the balloon therefore should be deflated and the catheter withdrawn to the right atrium for another attempt using very slow (e.g. 1 mm/sec) advancement.

5. After obtaining a wedge pressure, the balloon is deflated; deflation is confirmed by reappearance of pulmonary artery pressure contours. The balloon is reinflated with 0.6 to 0.7 cc air, and the catheter is slowly advanced a short distance until a wedge tracing is obtained. When wedge pressures are obtained with this amount of inflation, the catheter tip is usually in a satisfactory position. The balloon is deflated by removing the syringe; aspiration should not be used since this will occasionally destroy the air seal.

6. A portable chest x-ray is promptly obtained to ensure adequate catheter positioning. Before the cutdown site is closed, we attempt to place the tip 2–3 inches distal to the bifurcation of the pulmonary artery. With this positioning we have experienced little difficulty with the deflated catheter tip creeping out to a wedge position.

7. The catheter is secured to the forearm with tape. A stopcock manifold with the attached transducer is taped to the upper arm so that the zero reference stopcock is approximately midway between the anterior and the posterior chest with the patient supine.

8. The catheter is irrigated with a solution of 1,000 units of heparin per 500 cc fluid (usually 5% dextrose), using a continuous flushing system which allows for pressure recording and continuous small volume irrigation of 2–3 cc per hour (Sorenson Research Corp., Salt Lake City, Utah).

Potential Problems

The most frequent problem associated with the use of this catheter was rupture of the balloon which occurred in 20 cases (23%) after an average of 82 hours of continuous use. (One balloon lasted 275 hours before rupturing.) It should be noted, however, that the balloons were often inflated 50 times per day since multiple inflations were frequently used to verify a given wedge pressure.

In addition to the potential problems described above in the protocol, several other *avoidable* errors have been recognized:

1. Inaccurate wedge pressure measurements due to excessive balloon inflation *vide infra.*

2. Inaccurate pressure measurements due to damping of system. One must make sure there are no air bubbles in the fluid system. Also, we flush the system with 1–2 cc of fluid immediately before taking pressures to avoid partial occlusion at the end hole of the catheter.

3. Continuous wedge tracing with the balloon deflated. This occurs if the catheter tip advances distally so that the deflated tip itself completely occludes a branch of the pulmonary artery. If this develops, it is probable that either the tip was initially placed too far distally, or that excessive catheter "slack" was left in the right ventricle so that with successive balloon inflations the tip was progressively advanced by the flow of blood. Excessive "slack" in the catheter usually is caused by the catheter being advanced too rapidly through the right ventricle

and the pulmonary artery. If a spontaneous wedge tracing is seen while the balloon is deflated, the catheter tip must immediately be withdrawn until a pulmonary artery trace is obtained in order to avoid the possibility of pulmonary infarction.

4. Clotting of the catheter lumen. This was frequently encountered in our early experience. However, this has rarely been observed since using the continuous low volume irrigation system described above.
5. Leaving the balloon inflated after measuring a wedge pressure measurement.
6. Failure to deflate the balloon prior to withdrawal of the catheter.
7. Excessive administration of fluids in order to keep the catheter patent—prevented by continuous, low volume flushing device.

Results

The pulmonary artery was successfully catheterized in all patients. In one patient a wedge pressure tracing could not be obtained. While the procedure was easily performed in the majority of patients, 10–20% of the catheterizations were difficult and required more than 30 minutes. In one patient over three hours were expended before the catheter entered the pulmonary artery. All patients except one were catheterized without fluroscopy, using pressure contour monitoring only.

Morbidity and Complications

There were no deaths attributable to the procedure; however, several complications were observed:

1. One patient with an acute myocardial infarction developed ventricular fibrillation and was immediately defibrillated. Ventricular fibrillation may have been related to the undetected rupture of the balloon as it was inserted at the venotomy site with loss of the cushioning effect of the balloon in the right ventricle. It is likely that the balloon rupture in this case was due to the use of forceps while inserting the tip into the vein lumen.
2. Another patient, also with an acute myocardial infarction, required DC shock for an episode of sustained ventricular tachycardia which occurred with the catheter tip in the right ventricle.
3. Three patients had transient runs of ventricular tachycardia during passage of the catheter through the right ventricle.
4. Approximately 15% of the patients developed occasional ectopic ventricular depolarizations during catheterization.
5. One patient developed a localized abscess at the cutdown site; however this patient had ripped open the cutdown wound. This was the only recognized catheter related infection.

We have recognized no other complications such as pulmonary infarction, valve damage, catheter knotting, endocarditis, pulmonary hemorrhage, etc.

Clinical Application and Evaluation

Simultaneously recorded pulmonary artery wedge pressures (PAW) and central venous pressures (CVP) were compared in 54 patients in whom such pressures were serially monitored. The agreement* between PAW and CVP was poor in over one-third (39 per cent) of patients. Furthermore, this relationship between PAW and CVP, regardless of the absolute levels, was markedly inconstant during the long term monitoring period in nearly two-thirds (63%) of the patients. Figure 1 shows a representative example of "poor" correlation between CVP and PAW.

Similarly, examination of the relationship between PAW and near-simultaneous pulmonary artery diastolic pressure (PAD) showed a high degree of discrepancy. In only one-third (33%) of our patients were PAD and PAW divergent by 4 mm Hg or less in 90% of the comparative measurements. Differences between PAD and PAW exceeded 8 mm Hg in 44% of these 86 patients. Not only was PAD a poor reflection of PAW, but also this relationship was inconstant† in 41% of the patients. Figure 2 demonstrates a PAD-PAW relationship which at the initiation of monitoring was reasonably close. However, over the course of the following two days, this re-

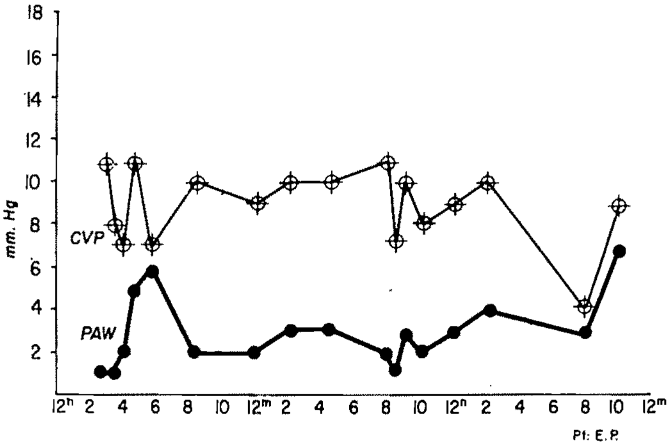

FIG. 1. Simultaneous pulmonary artery "wedge" (PAW) and central venous pressures (CVP) showing discrepant and inconstant relationship.

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* "Agreement" occurred when CVP and PAW were both normal, both high or both low. Normal limits of PAW were taken as 5–15 mm Hg; normal CVP was considered as 3–8 mm Hg. "Poor agreement" was defined as "agreement" in fewer than 50% of the simultaneously recorded pressures in a given patient.

† The relation between PAD and PAW was considered inconstant when the repeated difference between the simultaneously recorded pressures varied more than 6 mm Hg. For example, if the PAD-PAW difference was 8 mm Hg one hour and the difference between the two pressures was 18 mm Hg on a later reading, this would be considered to have an inconstant relationship.

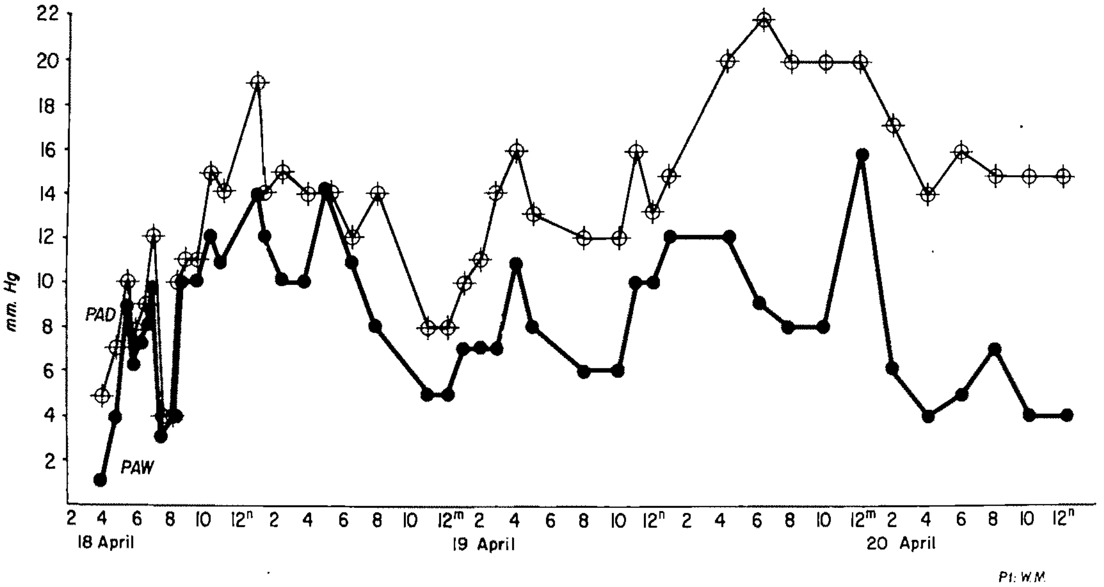

FIG. 2. Near-simultaneous pulmonary artery diastolic (PAD) and pulmonary artery "wedge" (PAW) pressure relationship which became progressively discrepant.

lationship became progressively discrepant and inconstant. During this two day period, the patient's clinical condition deteriorated substantially.

In our experience the Swan-Ganz catheter has provided an invaluable guide for the manipulation of intravascular volume in acutely ill patients.

Case Report

An illustration of this application is seen in the following case:

E.P. was a 55-year-old male who precipitously developed hypotension and oliguria shortly after surgery for bowel obstruction. The etiology of the patient's shock state was unknown. CVP ranged from 13–16 cm H_2O (10–12 mm Hg), and an infusion of norepinephrine was initiated to maintain a systolic blood pressure of 80–90 mm Hg. Diagnoses of myocardial infarction and pulmonary embolism were considered. The patient was transferred to the intensive care unit, and a Swan-Ganz catheter was promptly inserted. During insertion of the catheter right atrial pressure closely agreed with the CVP measurement. However, after passage into the pulmonary artery PAW was found to be extremely low (1 mm Hg), suggesting that the patient's major problem was intravascular depletion. The patient was immediately treated with large volumes of plasma and saline. This was followed by a prompt rise in systemic arterial blood pressure and reestablishment of urinary output, allowing the discontinuation of norepinephrine infusion-all within a 20-minute period.

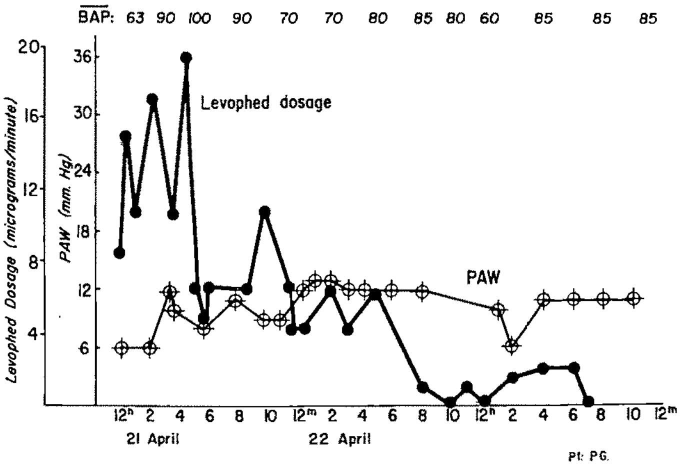

FIG. 3. PAW with norepinephrine infusion rate varying from 0 to 20 micrograms per min. Mean brachial artery pressure (BAP) is shown above. There is no apparent influence of norepinephrine on PAW.

Modifiers of PAW

There are factors other than the patient's volume status and ventricular function which may affect the PAW. Respiratory variation in pulmonary artery and PAW pressures may be appreciable, particularly in individuals with obstructive lung disease. Positive pressure ventilation commonly elevates these measurements, 5–10 mm Hg, or occasionally more. However, the quantitative effect of positive pressure elevation was variable, not only from patient to patient, but also in a given patient over a period of time. For the sake of consistency, we have recorded all pressure measurements with the patient momentarily off the ventilator whenever possible.

The possibility of vasoconstrictive agents affecting PAW was examined. It was of interest that in the 32 patients who were treated with either metaraminol or norepinephrine over periods of hours to days, there was essentially no elevation of the wedge pressures when the drugs were given in a dose such that the mean systemic arterial pressure did not exceed 100 mm Hg. Figure 3 illustrates the lack of effect of norepinephrine even when administered in large and variable doses over several days. In only two instances did the wedge pressure increase with the administration of these drugs. In both patients this rise occurred when inadvertently large doses of norepinephrine resulted in transient elevation of mean systemic arterial pressures approximating 150 mm Hg. It is probable that PAW elevation in these two patients resulted from an acute rise in left ventricular diastolic pressure secondary to the considerably increased afterload on the left ventricle.

An interesting observation was that related to the administration of intravenous furosemide. This drug, given in doses of 40 mg or more, commonly produced an immediate, but temporary, decrease in PAW. The reduction in PAW appeared unrelated to the diuretic effect of furosemide, and in 8 of 17 anuric patients, PAW fell significantly within 5–10 minutes after a single dose of furosemide. This effect usually lasted only 30–120 minutes, followed by return of PAW to previous levels. It is probable that this phenomenon relates to a peripheral vasodilating effect of the drug[2] with redistribution of blood volume from the central circulation to a peripheral pool. An example of this transient "medical phlebotomy" is shown in Fig. 4.

A significant and potentially common source of error involves a phenomenon we have termed "over-wedging." This phenomenon may occur when a small amount of additional air is introduced after the balloon has already been inflated sufficiently to obstruct flow in a branch of the pulmonary artery. In such a situation spuriously high "wedge" pressures may be recorded. "Over-wedging" has been seen with as little as 0.05 cc excess air (Fig. 5). Excessive balloon inflation results not only in a rise in the observed pressure but also affects the wedge pressure contour with progressive flattening. The mechanism involved in "over-wedging" is probably related to the over-inflated balloon, sealed against the lumen of the artery, extending distally and entrapping the catheter lumen through which pressure is measured.

Discussion

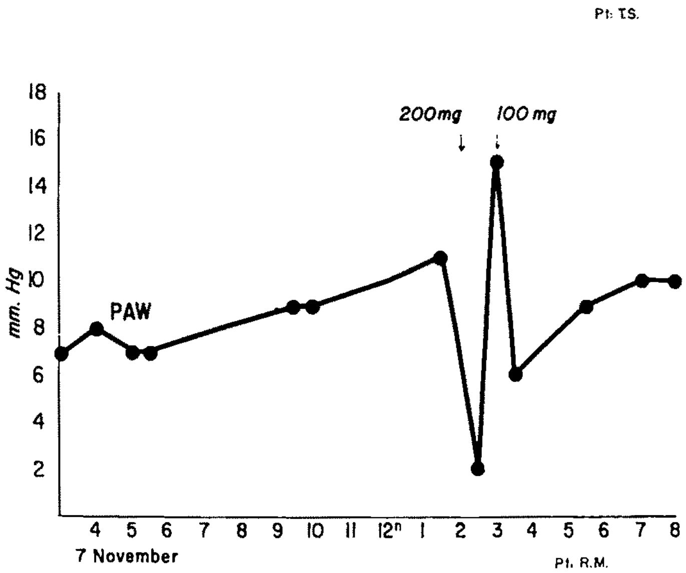

FIG. 4. Effect of intravenous furosemide (200 mgm and 100 mgm doses) on PAW in an anuric patient. Time is in hours.

Our observations as well as the experiences of others[3, 5,7] indicate that pulmonary artery and PAW pressure monitoring is practical and useful in the sequential evaluation of critically ill patients. Neither CVP nor pulmonary artery diastolic pressure is as reliable as PAW in estimating left atrial and pulmonary "capillary" pressure in critically ill patients. In cardiac patients PAW tends to be elevated relative to expected CVP.[3] Interestingly, in our group of predominantly non-cardiac patients, the lack of correlation between CVP and PAW was such that CVP was judged to be high relative to PAW in 74% of the patients who showed poor agreement. Presumably this reflects the frequency of lung disease and cor pulmonale in patients admitted to an intensive care unit. While pulmonary artery diastolic pressure may closely approximate PAW in normals and in some seriously ill patients, this relationship was discordant in the majority of our patients, markedly so in nearly one-half. Presumably this represented pulmonary arteriolar vasoconstriction due to hypoxia or other metabolic derangements—the resultant increase in pulmonary vascular resistance causing a rise in pulmonary artery diastolic pressure significantly above PAW.

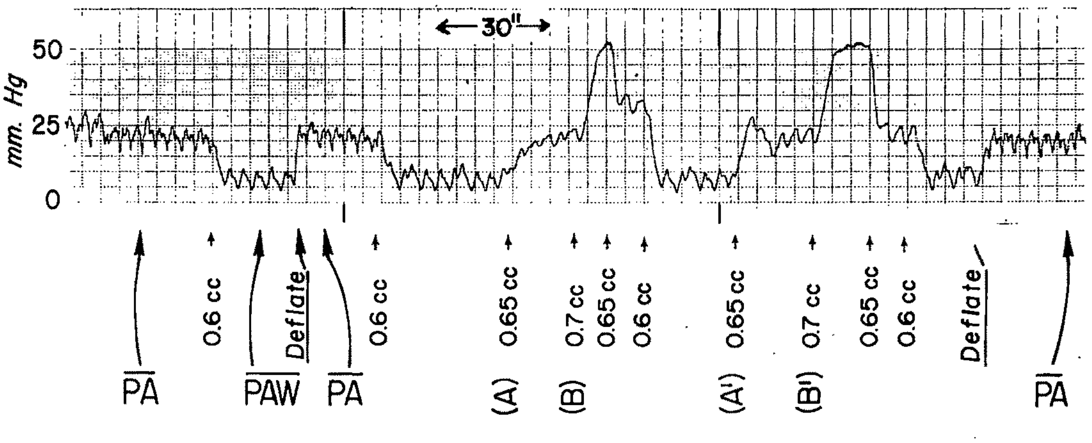

FIG. 5. Effect of excessive balloon inflation on mean PAW. Wedge pressure was observed after inflation with 0.6 cc air. An additional .05 cc resulting in a spuriously elevated pressure (A, A'). An additional increment of .05 cc produced an off-scale rise (B, B').

Although placement of the Swan-Ganz catheter is usually not difficult, there are several potential technical pitfalls. Most of these can be avoided by adherance to a meticulous technique for insertion and subsequent management. Perhaps the most serious technical error relates to the phenomenon of "over-wedging" with spuriously high pressures due to over-inflation of the balloon. This phenomenon can be avoided if one is aware of its possibility and mechanism and prevention.

Previous reports using this catheter have been con-concerned mainly with patients who have had acute myocardial infarction. In our judgment the Swan-Ganz catheter is an extremely useful adjunct in the assessment and management of intravascular volume and hemodynamic problems in all critically ill patients. The catheter is useful in the collection of mixed venous blood samples for calculation of cardiac output. We have also explored its application for small vessel pulmonary angiography; with the balloon temporarily inflated, 3–5 cc of contrast material is sufficient to produce detailed radiographs of segmental and smaller pulmonary arteries.

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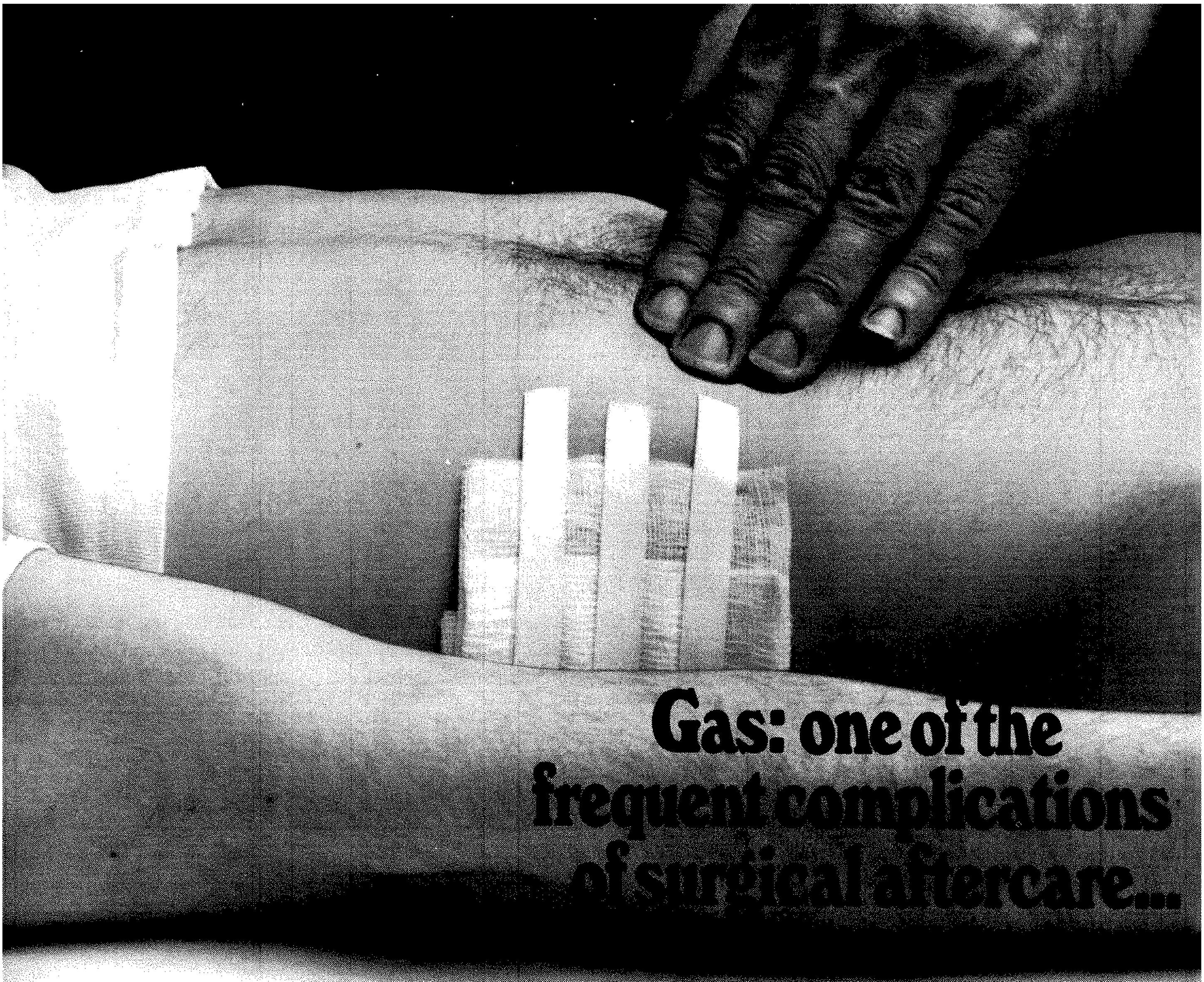
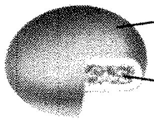


Painful gas accumulation in the gut, due to altered intestinal motility, aerophagia and increased salivation, often complicates surgical aftercare.

To help avoid or dispel the acute discomforts of post-op pain in the gut, Phazyme provides simethicone, *"...an effective, safe and simple method of preventing abdominal distention, gas pain and reducing the incidence of ileus."*[1]*



Phazyme's unique dual-phase action releases 20 mg. of specially-activated simethicone initially to the stomach for immediate dispersion of entrapped gas. The protected inner core delivers an additional 40 mg. of specially-activated simethicone to relieve pain of entrapped gas throughout the lower G.I. tract.

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol.* 38:386, Sept. 1971.
*Italics ours.

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prevents and relieves pain due to entrapped gas

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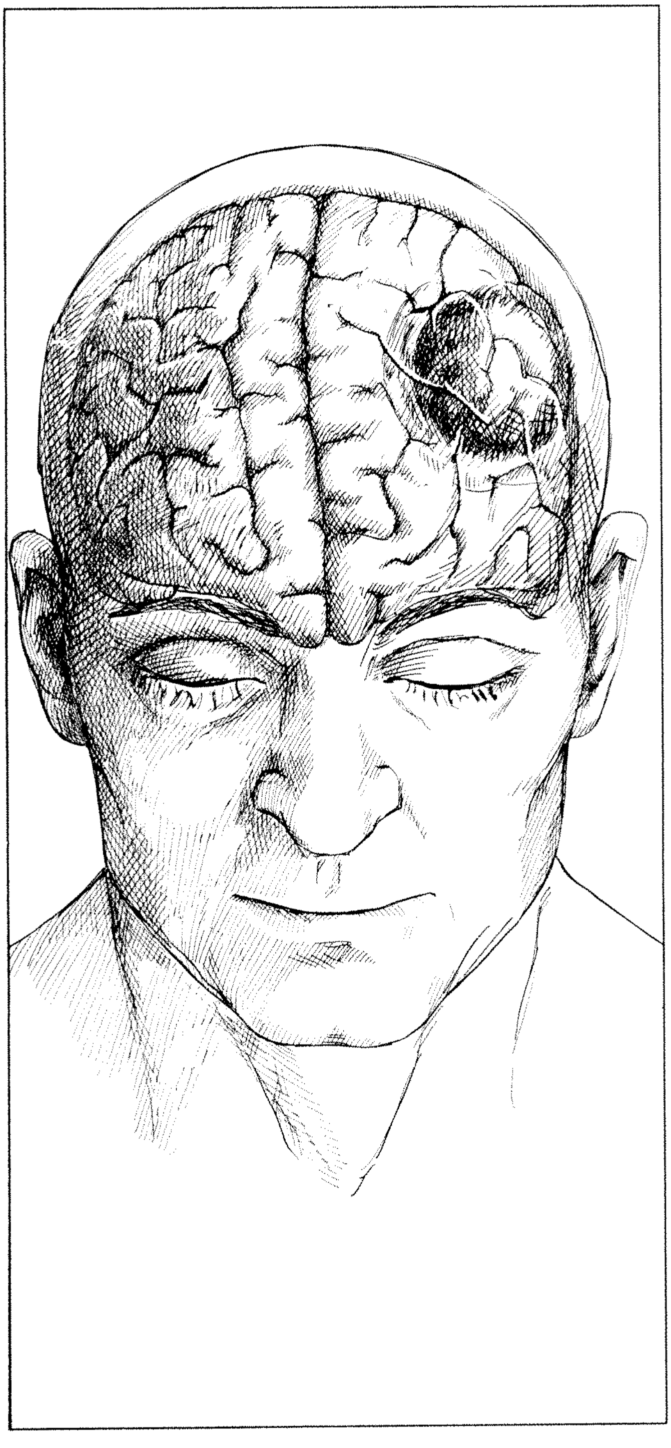
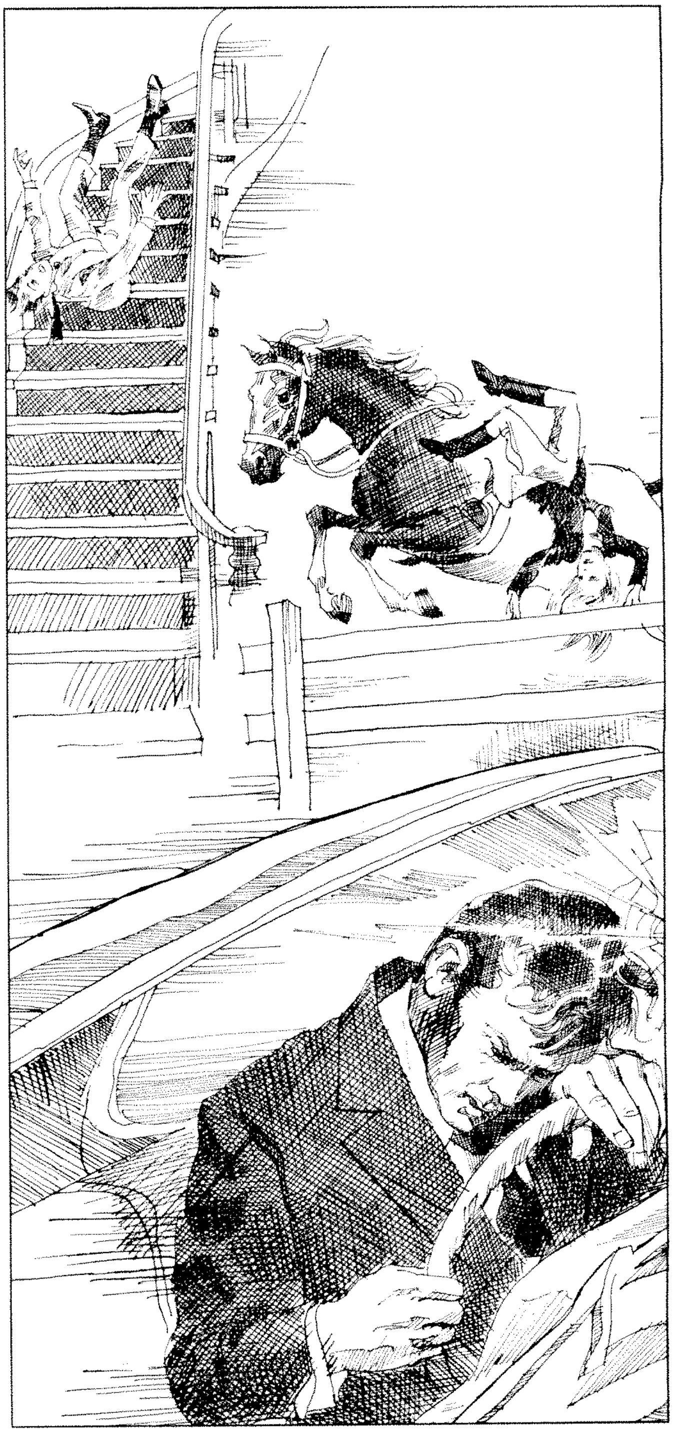
expect it as a possible complication of primary or metastatic brain tumor.

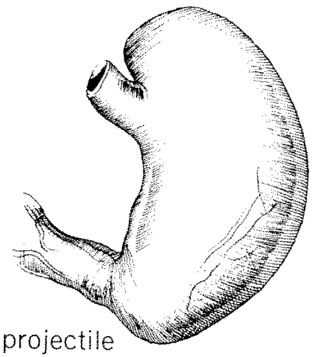


expect it in the presence of severe head injury.

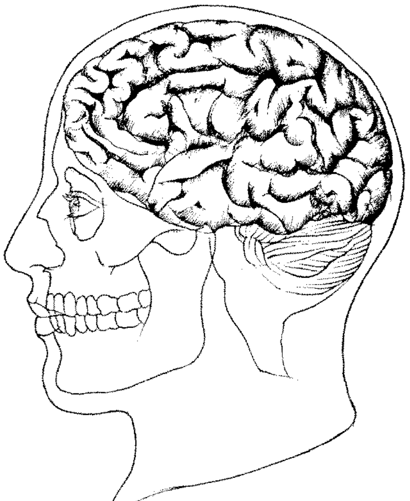


edema*

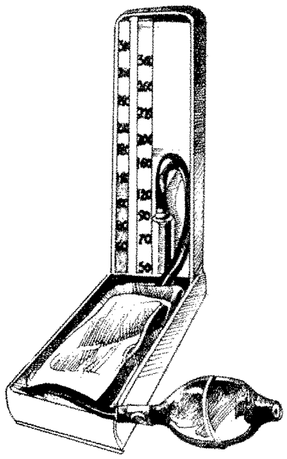
suspect it in the presence of signs and symptoms such as these:



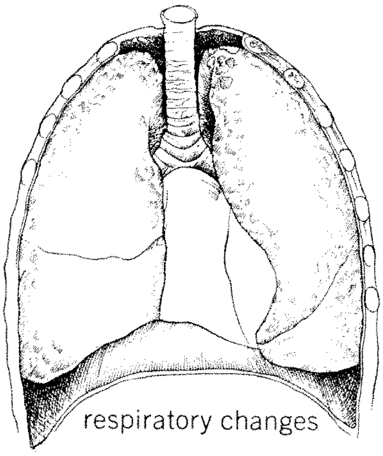
projectile vomiting



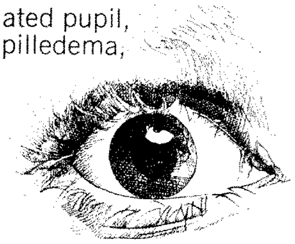
headache, altered consciousness



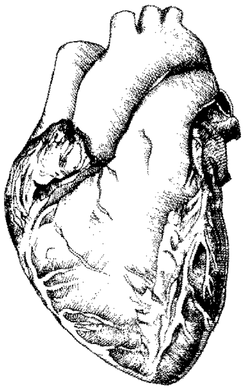
increased blood pressure



respiratory changes



dilated pupil, papilledema, unilateral or bilateral abducens palsy



bradycardia

***Note: The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.**

Injection: 4 mg/ml Phosphate

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Tablets: 1.5 mg, 0.75 mg, 0.5 mg, 0.25 mg

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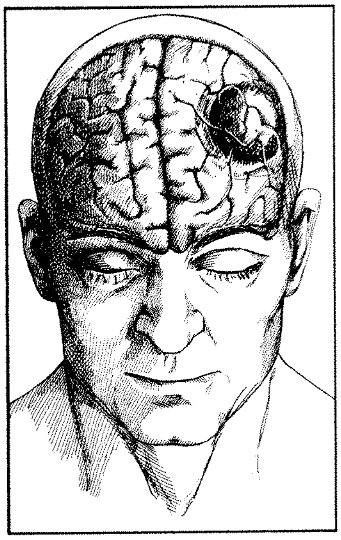
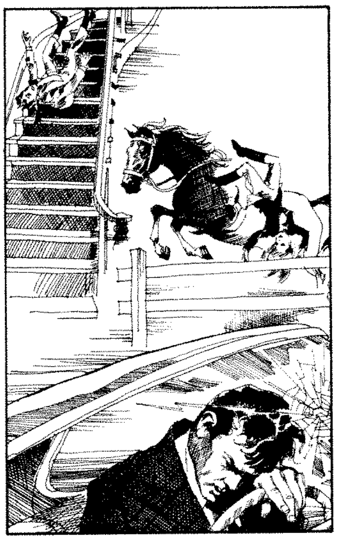
For a brief summary of prescribing information, please see following page.





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Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

Dosage for cerebral edema

Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

How Supplied: Tablets in four strengths: 1.5 mg dexamethasone, in bottles of 50; 0.75 mg dexamethasone, in 5-12 PAK® (package of 12), single-unit packages of 100, and bottles of 100 and 1000; 0.5 mg dexamethasone, in bottles of 100 and 1000; and 0.25 mg, in bottles of 100. Injection, in 1-ml disposable syringes and 1-ml, 5-ml, and 25-ml vials, containing per ml: dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone, 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, water for injection q.s. 1 ml, and 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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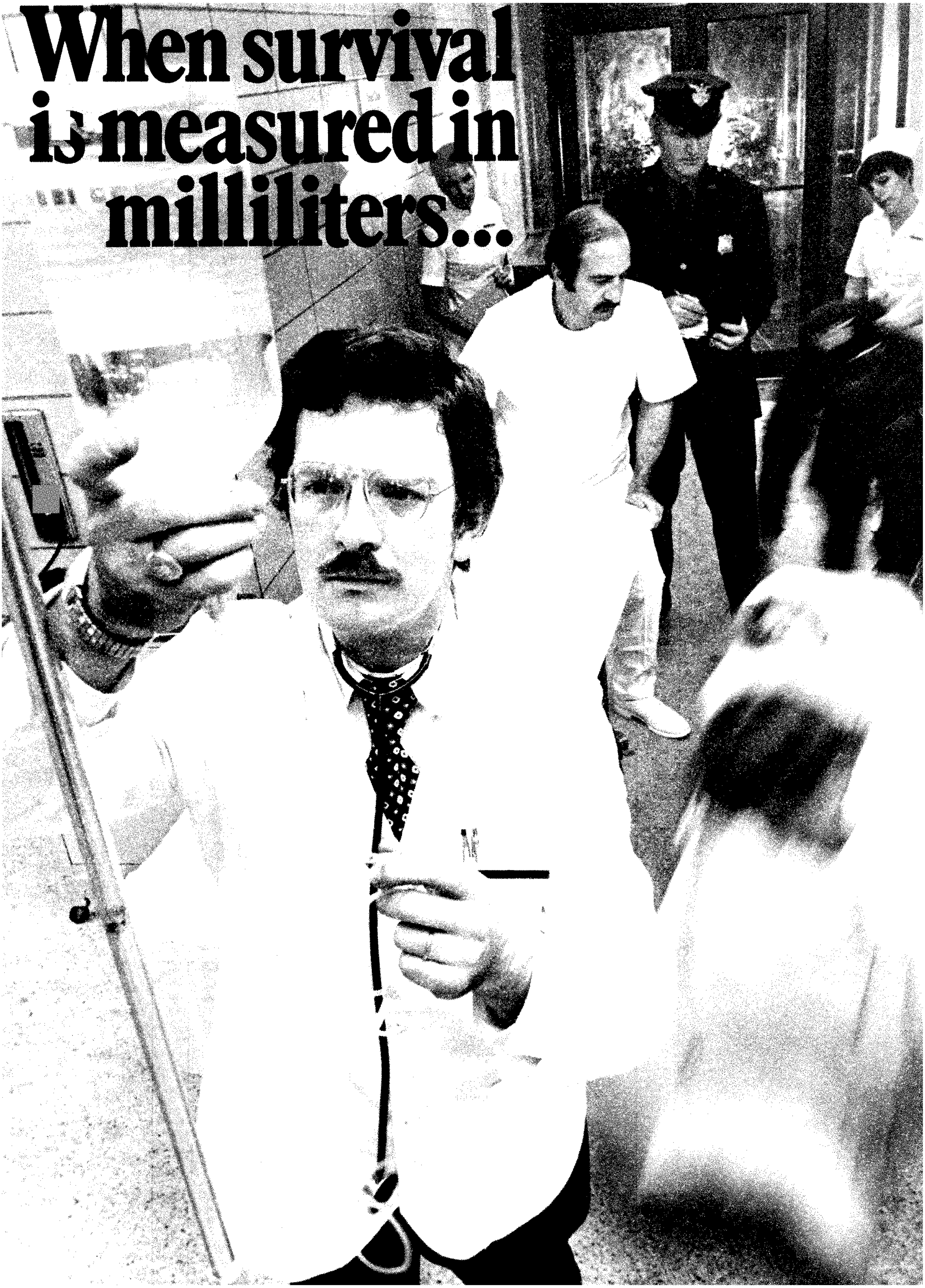
When survival is measured in milliliters...

Moments and milliliters... both are critical in treating hypovolemic shock since survival depends on the rapid, efficient restoration of circulating blood volume. Also crucial is the volume expander you use "stat." Rheomacrodex starts to work immediately to restore blood volume and adequate tissue perfusion.

Greater Initial Plasma Volume

In a recent study,[1] plasma volume expansion and cardiac output were measured in 36 patients with moderate or severe degrees of shock and in eight healthy subjects before, during and after infusion with 500 ml 10% dextran 40, whole blood, 6% dextran 70, plasma, and 5% dextran 40. The greatest plasma volume expansion was established in the 24 shock patients treated with Rheomacrodex. Peak plasma volume increases were more than one liter above controls. Plasma volumes decreased slowly as urinary output increased. Other studies also show the superiority of Rheomacrodex over blood, plasma, saline or lactated Ringer's for increasing initial plasma volume.[2-5]

Improved Cardiac Output

Measurement of hemodynamic effect revealed increased cardiac output directly related to increased volume expansion. Peak C.O. values occurred 15 minutes after Rheomacrodex infusion. In patients with moderate or severe degrees of shock, 10% dextran 40 increased cardiac output an average of 70% above control values.[1] Rheomacrodex improves hemodynamics—restores effective cardiac output and tissue perfusion—better than whole blood, plasma or clinical dextran.

Increased Tissue Perfusion

Restoring blood pressure often is not enough to reverse shock. Most important is the maintenance of adequate tissue perfusion. Rheomacrodex achieves this by decreasing red blood cell aggregation to a greater extent than crystalloids, blood or plasma.[6-10] This improvement in microcirculatory blood flow is reflected in increased oxygen availability and consumption, a vital contribution to the reversal of shock.[11]

Delayed Renal Excretion

In hypovolemia, delayed renal clearance tends to prolong the colloid osmotic effects of Rheomacrodex.[1] During infusion, Rheomacrodex is evenly distributed in the vascular system. The plasma concentration of dextran falls rapidly during the first hour as smaller molecules are excreted. Generally, 70% of Rheomacrodex infused in normovolemic subjects is excreted via the kidney in 24 hours.[12] Excretion is then slowed as the higher molecular weight fraction of dextran remains in the circulation to be metabolized at the rate of 70-90 mg/kg body weight per 24 hours.

Guidelines for Use

1. May be administered on a "response to therapy basis" up to 1,500 ml initially in first 24 hours.
2. Infuse first 500 ml within 30 minutes.
3. To support blood volume beyond 24 hours, administer 500 to 1,000 ml daily.
4. Do not continue beyond five days.
5. May be given with whole blood.
6. Keep patient well hydrated. Increase hydration if urine flow drops below 50 ml/hour.
7. Can be given to any patient without blood typing. However, blood should be drawn prior to infusion for future testing.

REFERENCES: 1. Shoemaker, W.C. and Monson, D.O.: Surg. Gynec. Obstet. 137:453, 1973. **2.** Ahnefeld, F.W. et al.: Anaesthesist 14:137 (May) 1965. **3.** Gelin, L.E. et al.: Acta Chir. Scand. 122:309, 1961. **4.** Gruber, U.F. et al.: Proc 10th Cong Int Soc Blood Transf., 1965, pp. 1116-1119, S. Karger, Basel (Switzerland). **5.** Gruber, U.F. et al.: Symposium on Rheomacrodex I (1964), pp. 13-23. **6.** Mainardi, L.C. et al.: Surgery 56:349 (Aug.) 1964. **7.** Martinovic, N. and Melrose, D.: J. Cardiovasc. Surg. 4:610 (Aug.) 1963. **8.** Suzuki, F. et al.: Ann. Surg. 160-263 (Aug.) 1964. **9.** Baker, R.J. et al.: Arch. Surg. 90:538 (Apr.) 1965. **10.** Baker, R.J. et al.: Arch. Surg. 89:373 (Aug.) 1964. **11.** Mohr, P.A. et al.: Circulation 39:379 (1969). **12.** Arturson, G. and Wallenius, G.: Scand. J. Clin. Lab. Invest. 16:81, 1964.

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(dextran 40)

For greater blood volume...faster

CONTRAINDICATIONS: Hypersensitivity to dextran. Marked hemostatic defects of all types. Marked cardiac decompensation. Renal disease with severe oliguria or anuria.

WARNINGS: Severe and fatal anaphylactoid reactions may occur infrequently during the early part of the first infusion of dextran. If such reactions appear imminent, stop infusion immediately. Since dextran draws water from extravascular space, give dehydrated patients additional fluids (degree of dehydration can be assessed by serum or urine osmolarity). Diuretics may be used to maintain adequate urine flow. Renal failure, sometimes irreversible, osmotic nephrosis, and, occasionally, abnormal hepatic and renal function values have been reported. Because safety in early pregnancy has not been established, do not use in women of childbearing age unless potential benefits outweigh risks. Use cautiously in patients with active bleeding.

PRECAUTIONS: Doses up to 15 ml/kg may produce small changes in coagulation; factor VIII may decrease markedly, but bleeding time is only rarely prolonged significantly. Observe all patients for early signs of bleeding complications. Monitoring of central venous pressure may help avoid circulatory overloading. Do not depress hematocrit below 30 vol. %. Dextran interference with blood glucose determinations, some blood typing and cross matching procedures and bilirubin and protein assays can be avoided by drawing blood samples pri giving Rheomacrodex or by informing lab that Rheomacrodex has been given so that suita assay methods can be used.

ADVERSE REACTIONS: Hypersensitivity reactions, which occur infrequently, can range fro mild cutaneous eruptions to generalized urticaria, nausea and vomiting, tightness of the cl wheezing, and, rarely, to anaphylactoid (allergic) shock. If any such reactions appear, start appropriate countermeasures promptly.

DOSAGE: Total dosage should not exceed 20 ml /kg in the first 24 hours or 10 ml /kg in eac subsequent 24 hours. Do not continue beyond 5 days.

SUPPLIED: Bottles of 500 ml 10% solution in normal saline or in 5% aqueous dextrose.

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Whenever an APC/narcotic is indicated

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INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS: *Drug Dependence:* Oxycodone can produce drug dependence of the morphine type and, therefore, has the potenti for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of Percodan, and i should be prescribed and administered with the same degree of cautio appropriate to the use of other oral narcotic-containing medications Like other narcotic-containing medications, Percodan is subject to th Federal Controlled Substances Act.

Usage in ambulatory patients: Oxycodone may impair the mental and/o physical abilities required for the performance of potentially hazardou tasks such as driving a car or operating machinery. The patient usin Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patient receiving other narcotic analgesics, general anesthetics, phenothiazines other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CN depression. When such combined therapy is contemplated, the dose o one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been establishe relative to possible adverse effects on fetal development. Therefore Percodan should not be used in pregnant women unless, in the judgmen of the physician, the potential benefits outweigh the possible hazards

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulce or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* Th respiratory depressant effects of narcotics and their capacity to elevat cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increas in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with hea injuries.

Acute abdominal conditions: The administration of Percodan or othe narcotics may obscure the diagnosis or clinical course in patients wit acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certai patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken i excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting Some of these adverse reactions may be alleviated if the patient lies down

Other adverse reactions include euphoria, dysphoria, constipation an pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It ma occasionally be necessary to exceed the usual dosage recommende below in cases of more severe pain or in those patients who have becom tolerant to the analgesic effect of narcotics. The usual adult dose is on tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan ma be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effec of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Seriou overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscl flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arres and death may occur. The ingestion of very large amounts of Percoda may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the reestablishment o adequate respiratory exchange through provision of a patent airway an the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes agains respiratory depression which may result from overdosage or unusua sensitivity to narcotics, including oxycodone. Therefore, an appropriat dose of one of these antagonists should be administered, preferably b the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that o the antagonist, the patient should be kept under continued surveillanc and repeated doses of the antagonist should be administered as neede to maintain adequate respiration.

An antagonist should not be administered in the absence of clinicall significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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See facing page for Brief Summary

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

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when pain goes on...

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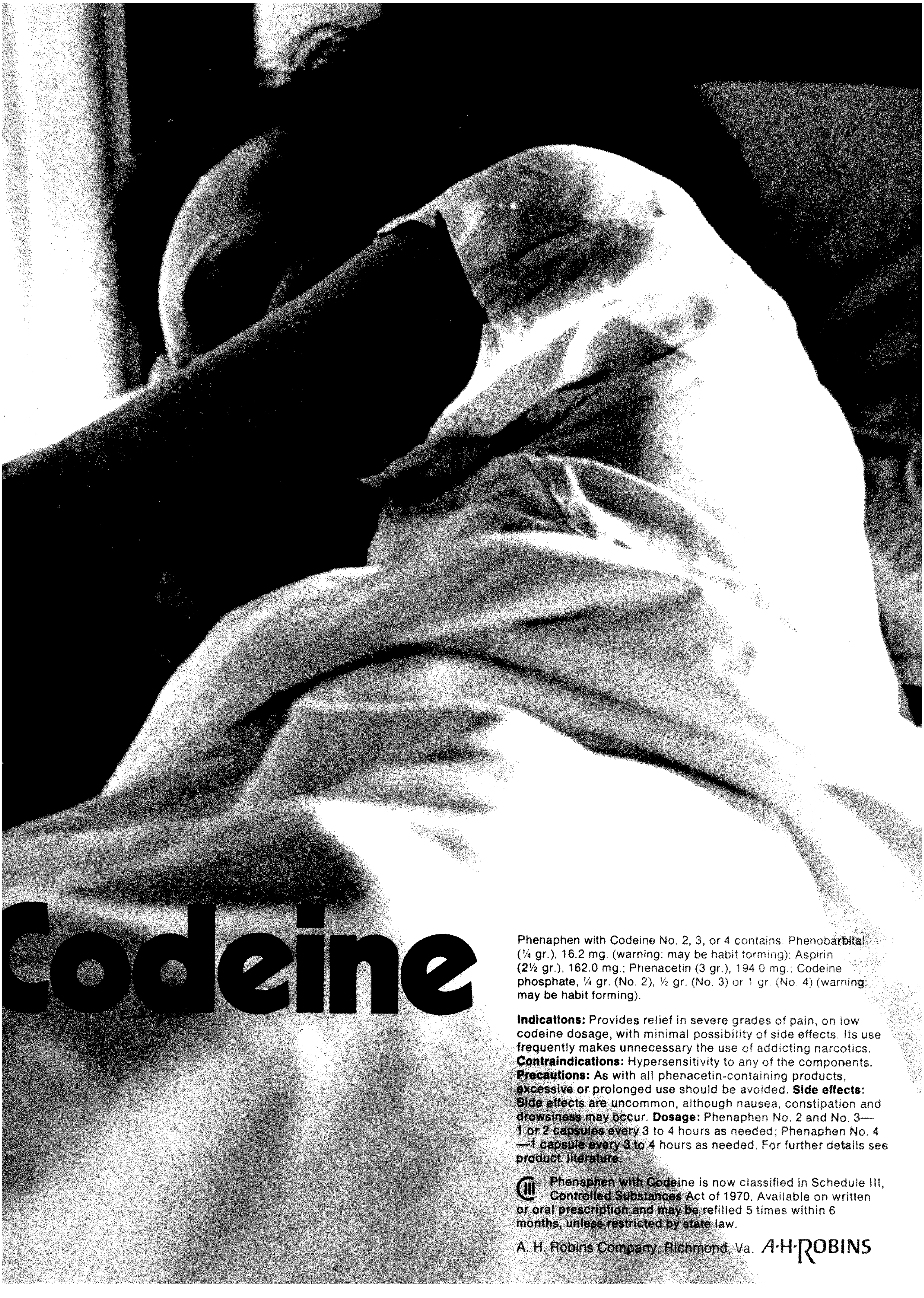
nd on–

e analgesic formula that calms instead of caffeinates

Phenaphen®

r the patient with a terminal illness, PAIN past, present, and future can dominate s thoughts until it becomes almost an obsession. The more he is aware of the pain is now experiencing, the more difficult it is to erase his memory of yesterday's in, and to allay his fearful anticipation of tomorrow's pain.

rely the last thing this patient needs is an analgesic containing caffeine to stimulate e senses and heighten pain awareness. A far more logical choice is Phenaphen th Codeine. The sensible formula provides ¼ grain of phenobarbital to take e nervous "edge" off, so the rest of the formula can help control the pain more fectively. Don't you agree, Doctor, that psychic distress is an important factor most of your terminal and long-term convalescent patients?



Codeine

Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

Indications: Provides relief in severe grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

Ⓒ III Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

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Ask the operating room nurse and she will have already heard from all, or most of the above-mentioned people. She might even remark that she doesn't really care whether the viewing port's on the top or bottom. It's the controlled graduated compression she appreciates.

Ask the purchasing agent and he will know plenty about READIFLEX Stockings. Then, when you tell him the prices of READIFLEX Stockings, he'll warm right up. And, when you reveal the viewing port is on top, perhaps a very small smile will begin playing around the edges of his mouth. Especially when you remind him he'll only have 3 sizes to stock.

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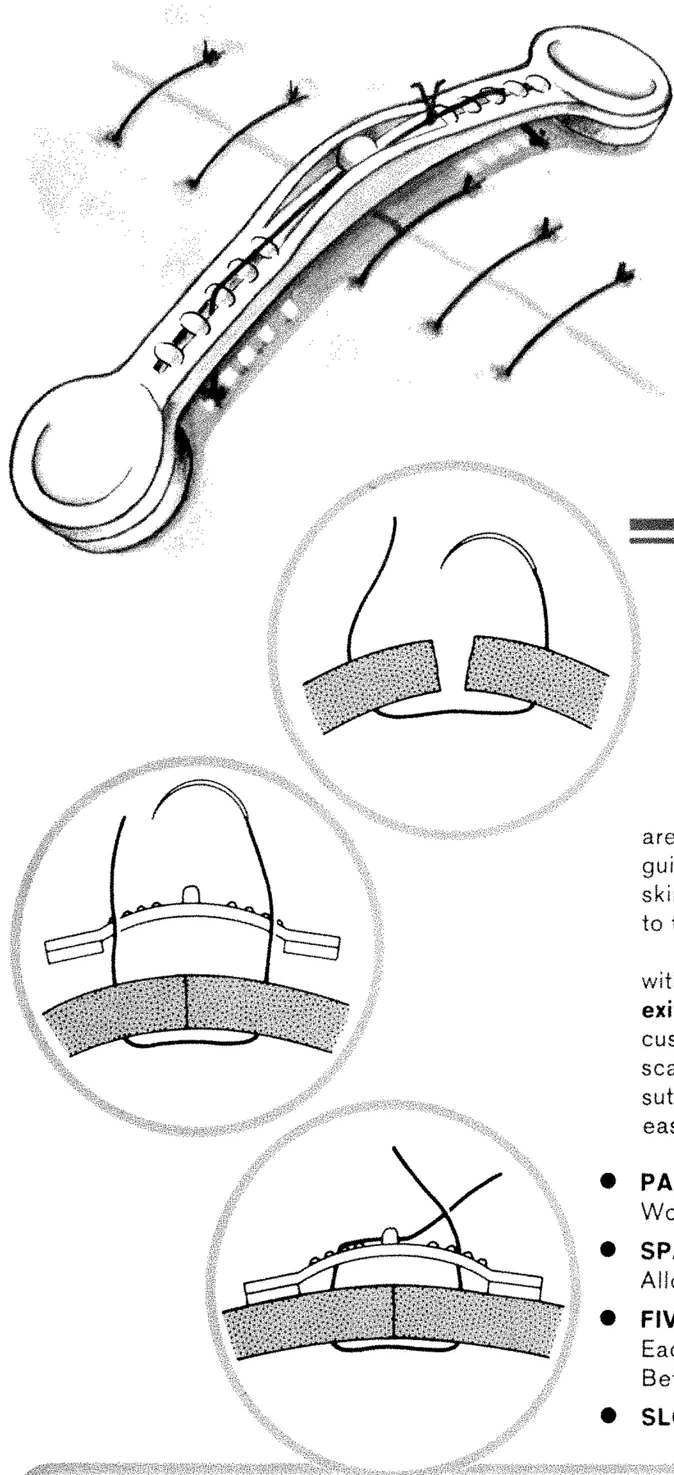

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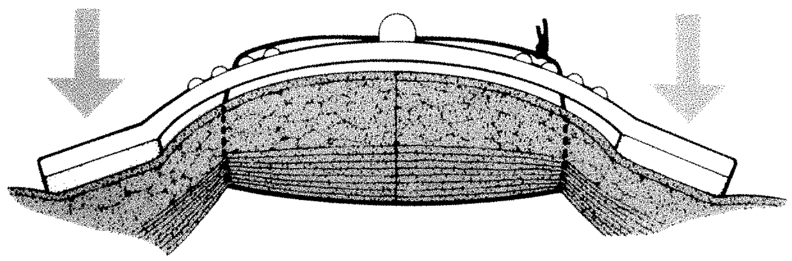

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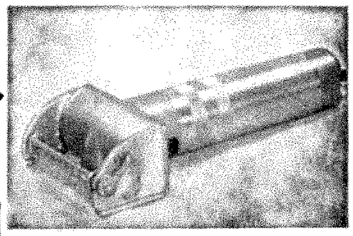

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*Oil-soluble vitamins A, D and E water solubilized wit sorethytan laurate; covered by U.S. Patent No. 2,417,299.

BRIEF SUMMARY

INDICATIONS: *in emergency feedings*—Surgery, extensive burns, fractures and other trauma, severe infectiou diseases, comatose states, etc. may provoke a "stress" si uation with profound alterations in the body's metaboli demands and consequent tissue depletion of nutrients. As result, wound healing may be impaired, enzyme activity dis turbed, hematopoietic tissues affected; hypoproteinemi and edema may appear; convalescence is thus prolonged. In such patients M.V.I. (administered in intravenous fluid under proper dilution) contributes optimum vitamin intak toward maintaining the body's normal resistance and repa processes.

DIRECTIONS FOR USE: M.V.I. is ready for immediate us when added to intravenous infusion fluids.
For intravenous feeding, one daily dose of 10 cc. of M.V.I. c 5 cc. of M.V.I. Concentrate added directly to not less tha 500 cc., preferably 1,000 cc., of intravenous dextrose, salin or similar infusion solutions...plasma, protein hydrolysates etc.

PRECAUTION: Allergic reaction has been known to occu following intravenous administration of solutions containin thiamine.

CAUTION: Not to be given as a direct undiluted intravenou injection as it may give rise to dizziness, faintness, etc.

THERAPEUTIC NOTE: Intravenous use should be discon tinued as early as practical in favor of an intramuscular c oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.—10 cc. ampuls, boxes of 25 an 100.
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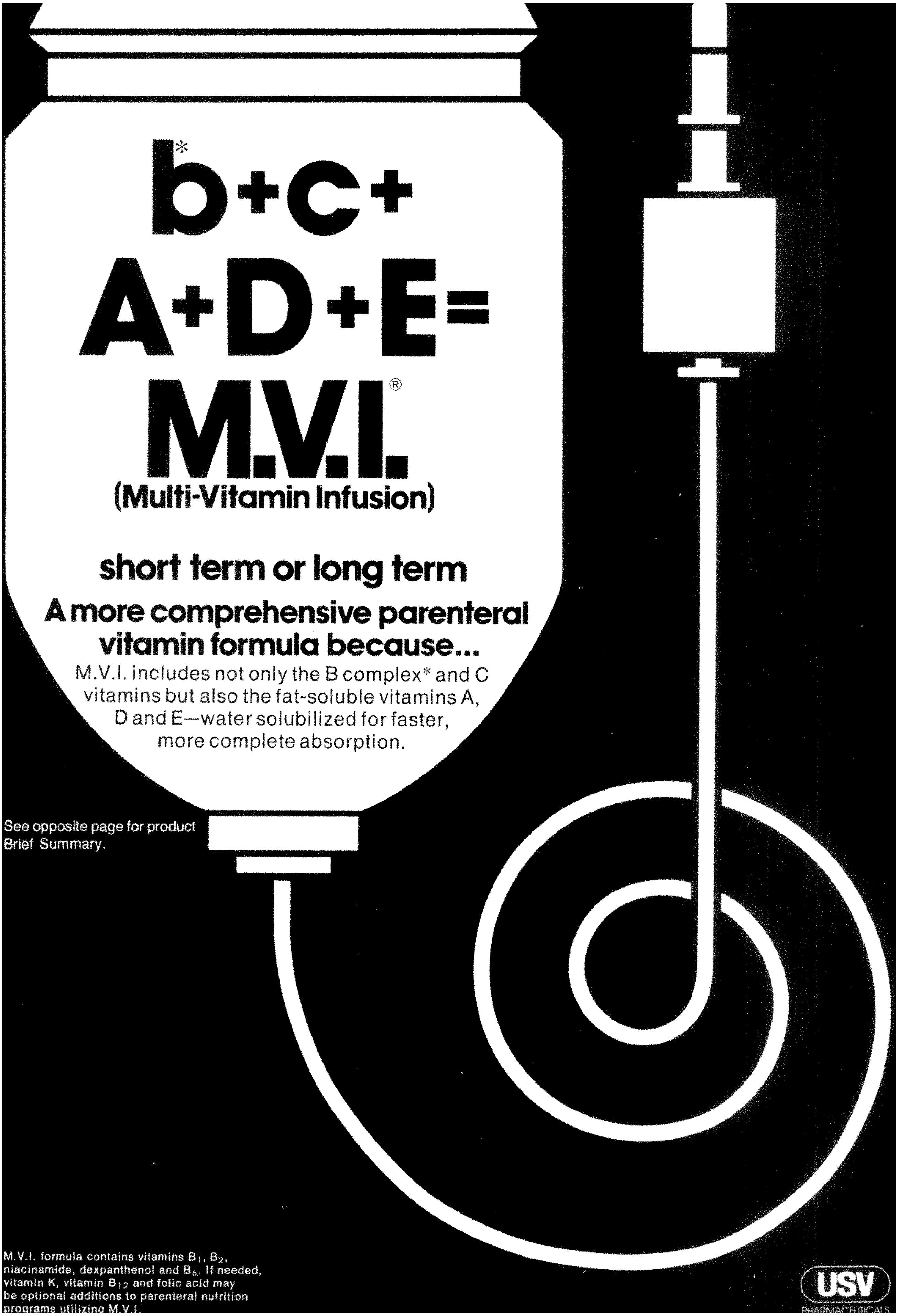

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See opposite page for product Brief Summary.

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Histopathology of One-stage Bilateral Lung Allografts

YOSHIO KONDO, M.D., JOHN V. COCKRELL, M.D., OSAMU KUWAHARA, M.D.,
JAMES D. HARDY, M.D.

From the Department of Surgery, The University of Mississippi Medical Center, Jackson, Mississippi

Morphological features of modified and unmodified bilateral lung allografts were studied in 87 dogs. Immunosuppressive treatment consisted of various combinations of azathioprine, methotrexate, prednisolone, methylprednisolone and antilymphocyte serum. The classic acute rejection was observed in the unmodified dogs, which died between 4 and 9 days. Progression of the lesion was confined to a certain stage in these lung allografts charged with providing total pulmonary function, so that hemorrhagic necrosis was never encountered. Immunosuppressive drugs decrease the speed and intensity of classic rejection, and increase the complications of respiratory infection in the protracted course. Of 14 dogs surviving more than 14 days, 4 died of chronic rejection at 72, 84, 177, and 396 days after transplantation. Death of the remaining animals was attributed to acute rejection (3 dogs); severe anemia (3 dogs); pulmonary infection and sepsis (3 dogs); and arterial thromboembolism (1 dog). In these long-functioning lung allografts, the alveolar lining cells were frequently replaced by very atypical cells presumed to be type 2 pneumocytes. The bronchus was occluded by mucus plugs, and the alveolar surface was covered with hyaline membrane, or obliterated by organized fibrocellular precipitate. The alveolar walls and perivascular area were thickened by fibrosis. Obliterative intimal thickening of pulmonary arteries was not observed. Although the immunologic and non-immunologic mechanisms responsible for the development of these lesions are difficult to separate, these cumulative changes apparently accompany the deterioration of the vital function of the graft until ultimate death.

SINCE MOST REPORTED STUDIES on the morphological features of lung allografts have been done following unilateral transplantation,[1–5,8–10,12,19,23,24] it was difficult to correlate the observed changes with actual functional capacity of the allografts. Various methods of obligatory lung allotransplantation, such as unilateral allotransplantation with staged contralateral pneumonectomy or unilateral allotransplantation with ligation of the contralateral pulmonary artery, have been attempted recently,[5,6,11,26] but survival beyond three months has not been reported. We previously reported experimental studies in one-stage bilateral allotransplantation of the canine lungs with regard to technical details, unmodified rejection reaction, immunosuppression, and scanning and transmission electron microscopy.[14–16] The present report describes the histopathologic characteristics of the canine lung allograft which has totally sustained respiratory function for periods from 4 to 396 days after bilateral allotransplantation.

Materials and Methods

Pairs of adult mongrel dogs of equal size were utilized. Bilateral allotransplantation of the lung was performed as a one-stage procedure of successive right and left lung transplantation by separate thoracotomy.[14,15] The entire series of 87 dogs was divided into three groups based on differences in the immunosuppressive regimen. The animals in Group I received no immunosuppressive drug (Control group). The dogs in Group II were treated with one of three combinations of immunosuppressive drugs: 1) azathioprine and prednisolone, 2) methotrexate and prednisolone, and 3) antilymphocyte globulin, prednisolone and azathioprine or methotrexate. Azathioprine was administered orally with an initial dosage of 4–5 mg/kg daily for 2 weeks, 3 mg/kg daily for the next 2 weeks, 2 mg/kg daily for the next 4 weeks, and 1 mg/kg daily as the maintenance dosage. Methotrexate was administered intramuscularly, 0.4–0.5 mg/kg every other day for the first 2 weeks, and was gradually reduced to the maintenance dosage of 0.1 mg/kg once a week. The

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daily dosage of prednisolone (subcutaneous injection) was the same as that of azathioprine. Antilymphocyte globulin was given intramuscularly for 2 weeks, 1 ml/kg daily, starting 1 day before transplantation. The dogs in Group III were treated with a combination of azathioprine, methylprednisolone and antilymphocyte serum in approximately half the dosage of each drug used in Group II. The azathioprine dosage was 2.5–3.0 mg/kg daily for the first week, 2.0 mg/kg daily for the next 2 weeks and 1.0 mg/kg daily or less as the maintenance dosage. Methylprednisolone was administered at a level of 6.0–7.0 mg/kg immediately after operation, and in the same dosage as azathioprine thereafter. Antilymphocyte serum was given intramuscularly starting 2 days before transplantation, 0.5 ml/kg daily for 2 weeks, and continuing for 3 months with gradually diminishing regularity. Antibiotics (penicillin-streptomycin and/or chloramphenicol) were administered for 2 weeks postoperatively.

Eight of 9 dogs (89%) in Group I, 32 of 47 dogs (68%) in Group II, and 28 of 31 dogs (90%) in Group III tolerated the procedure and lived more than 3 days. These animals form the basis of this analysis.

Open lung biopsies were performed in selected cases. Biopsy specimens from 5 dogs living 2–3 years after bilateral lung reimplantation were included for comparison. All animals were autopsied immediately after death. The heart and lungs were excised *en bloc,* and the lungs were inflated with 500 ml of 10% formalin infused through the trachea into the bronchi. To distinguish between the small arteries and the veins, some of the lung grafts were injected with a suspension of barium sulfate into the pulmonary artery, which will fill small arteries without entering the venous circulation. Paraffin sections from many areas of the lung lobes, as well as samples of the heart, liver, kidney, spleen and bone marrow, were stained with hematoxylin-eosin in all samples, and frequently with elastic tissue and trichrome stains. Immunofluorescent technique was performed in frozen sections of the grafts which were obtained either by biopsy or immediate postmortem autopsy. Details of the method, including the preparation of rabbit antidog-IgG and -IgM, are described elsewhere.[18]

Results

All 8 dogs in Group I died between 4 and 9 days after transplantation. In Group II 16 dogs survived more than 7 days and of these, 6 lived more than 14 days; the longest survival was 396 days. In Group III, 14 dogs survived more than 7 days, with 8 surviving more than 14 days.

Table 1 summarizes the frequency of occurrence of major pathologic changes being detailed here. The ultimate conditions of the animals in the entire series are discussed according to three categories of reaction.

Acute Rejection Observed in Unmodified Dogs

The classic type of acute rejection was observed in the unmodified dogs of Group I. Autopsy revealed severely enlarged, uniformly consolidated, poorly aerated, congested lungs; the bronchial tree was filled with frothy, hemorrhagic exudate. Arterial and atrial anastomoses were healing satisfactorily. In contrast, inadequate blood supply to the bronchial wall of the graft frequently caused extensive necrosis of the mucosa, sloughing of the cartilage, and even partial necrosis of the entire wall distal to the anastomosis.

Microscopically, there was demonstrated advanced mononuclear cell infiltration predominantly around the small vessels, alveolar ducts, and bronchioles. Arterial infusion of barium sulfate suspension in the area exhibiting a relatively mild degree of rejection clearly showed that the change started around the small veins in the peripheral area of the lobe, while the small arteries and the major structures remained almost free of involvement (Fig. 1A). Many of the infiltrating cells appeared to be

TABLE 1. *Summary of Pathologic Changes in Bilateral Lung Allografts*

	Number of Dogs	Pathologic Changes				
		Mononuclear Infiltration	Alveolar Edema	Pneumocyte Change	Pulmonary Fibrosis	Broncho-pneumonia
Group I (N = 8)						
14–7 days	1	1	1	0	0	0
7–3 days	7	7	7	0	0	4
Group II (N = 32)						
> 28 days	4	0	1	3	3	3
28–14 days	2	2	2	2	0	1
14–7 days	10	3	8	0	0	8
7–3 days	16	3	12	0	0	13
Group III (N = 28)						
> 28 days	5	1	2	4	4	2
28–14 days	3	1	1	2	0	2
14–7 days	6	6	6	2	0	4
7–3 days	14	6	12	0	0	12

Number under Pathologic Changes indicates the number of dogs showing moderate to severe lesions of these types.

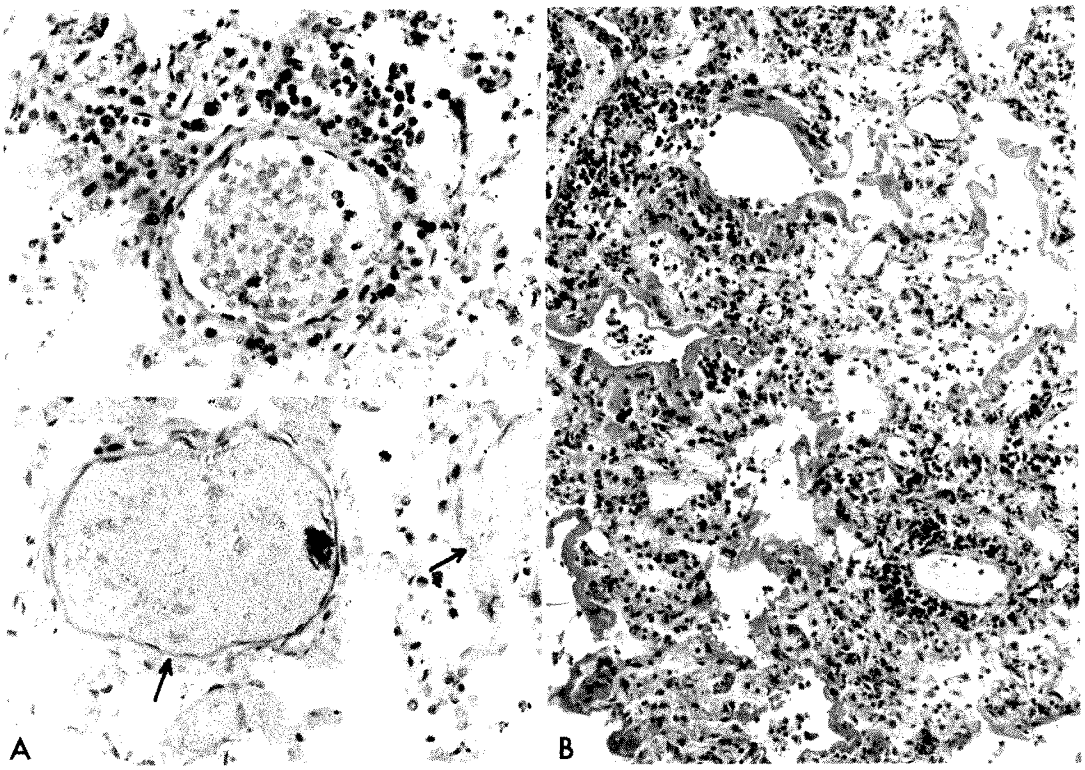


FIG. 1. Acute rejection observed in unmodified dogs. A. Initial stage of mononuclear cell infiltration is seen around the small vein, but not around the small artery (filled with barium sulfate, and indicated by arrows) at 5 days post-transplant (hematoxylin-eosin, original magnification × 133). B. Advanced mononuclear cell infiltration with hyaline membrane formation at 9 days post-transplant (hematoxylin-eosin, original magnification × 33).

large and small lymphocytes with frequent plasma cells and monocytes. There were fluorescent IgG- and IgM antibodies in the cytoplasm of some of these cells. Similar mononuclear cell infiltration also involved the alveolar septa, veins and bronchial walls to varying extents, but consistently spared the arterial walls. The alveolar septa were severely edematous and congested, and large numbers of alveolar macrophages were frequently observed. Terminally, there was extensive loss of bronchial epithelium, and plugging of the bronchi with an apparent mixture of mucus, fibrin and cell debris. These changes were generally associated with intraalveolar edema, and in some areas with cuboidal transformation of the alveolar and alveolar duct lining cells and intraalveolar hemorrhage. Proteinaceous exudate lined the alveoli in certain areas, developing the microscopic appearance of hyaline membrane formation (Fig. 1B). Thus, respiratory insufficiency with clinical signs of acute pulmonary edema due to acute rejection caused the deaths of 4 dogs, and in the remaining 4 animals the above mentioned changes were complicated with varying degrees of bronchopneumonia. Hemorrhagic necrosis of the lung, reported to be a far-advanced rejection process following unilateral allografting, was not observed in our animals.

Acute Rejection Observed in Animals Receiving Immunosuppressive Drugs

Some of the dogs which died within 2 weeks in Groups II and III showed similar features of acute rejection as described above. The main difference from the control animals was the variety in speed and intensity of the pathologic process. Actually, most dogs in this category died of infectious complications before acute rejection reached a late stage. There was usually minor to moderate mononuclear cell infiltration; this change was better suppressed in the animals of Group II than in those of Group III. Signs of pulmonary edema progressed much more slowly, and the alveolar exudate contained a richly fibroproteinaceous material, leading to pathologic manifestation of hyaline membrane formation. Alveolar septa were thickened by edema and congestion, and severe perivascular edema with dilated lymphatics was prominent in the samples from 7–14 day survivors (Fig. 2). These changes were modified ominously with increasing degrees of bronchopneumonia.

Changes Observed in the Prolonged Survivors

Six dogs of Group II and 8 dogs of Group III, which survived more than 14 days, were included in this category. Table 2 shows the survival time of these dogs and the cause of death based on clinical symptoms and autopsy findings. Four dogs died of delayed acute rejection. Severe anemia, which was probably caused by drug intoxication, killed 3 dogs; the grafts of these dogs showed only mild changes. Four dogs died of chronic rejection at 396, 177, 84, and 72 days respectively, and the grafts demonstrated severe obliteration of the normal pulmonary architecture. The longest survivor exhibited a generalized plasma cell reaction and infiltration simulating generalized multiple myeloma in the human. In the

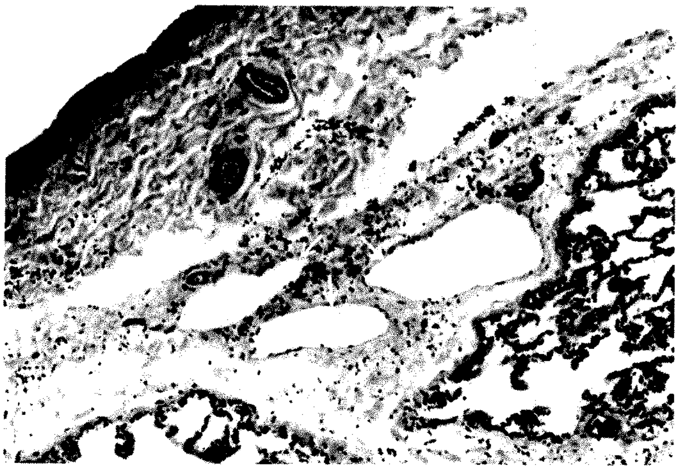


FIG. 2. Section from a 13-day survivor reveals severe perivascular edema with dilated lymphatics (arrows). (Hematoxylin-eosin, original magnification × 33).

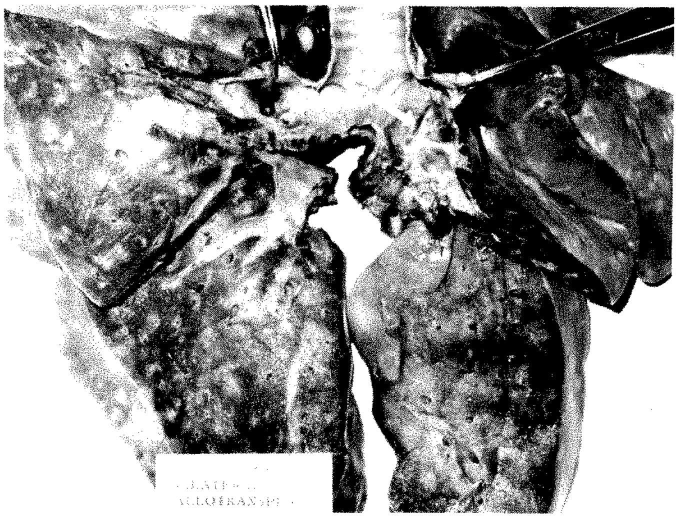


FIG. 3. Bilateral lung allografts of an attenuated survivor (47 days) showing the pleural surface, cut surface and well-healed bronchial suture lines (arrows). Marked degree of consolidation in hilar area.

remainder, autopsy revealed a partially consolidated, anemic lung with increased resistance to inflation (Fig. 3). Some bronchi and bronchioles were occluded by mucus plugs, causing patchy atelectasis in the periphery. Microscopically, the bronchiolar and alveolar lumens were frequently obliterated by organized precipitates containing fibroproteinaceous materials, desquamated epithelial cells, infiltrating blood cells and reactive macrophages (Fig. 4). The alveolar septa were thickened, presumably by organizing interstitial edema fluid and reacting connective tissue (Fig. 4). Some of the alveolar capillaries were congested, but many of them appeared relatively bloodless. Perivascular and peribronchial mononuclear cell infiltrations were seen in localized areas and occasionally involved the vascular and bronchial walls as well, leading to narrowing or obstruction of the small lumen. Perivascular fibrosis was frequently observed in variously-sized vessels. Despite such vascular involvement, we never identified fibrinoid necrosis of the vascular wall. Internal elastic lamellae of the medium and large pulmonary arteries were well preserved, and obliterative intimal thickening was seen only rarely, if indeed at all (Figs. 5A, B).

Obviously, such lungs were extremely vulnerable to infection under the influence of continuous immunosuppressive therapy. Delayed healing of the bronchial suture line added further difficulties. Thus, various grades of acute and chronic bronchopneumonia coexisted with the aforementioned changes.

Another distinct feature was the presence of a large number of very atypical, reactive appearing cells in the alveolar spaces. These cells contained very large nuclei with a peripheral condensation of chromatin and extremely large and prominent nucleoli. Cytoplasm was abundant and frequently vacuolated. Some of these cells

TABLE 2. *Cause of Death in the Prolonged Survival Category of Canine Bilateral Lung Allografts*

Survival Time	Cause of Death
Group II	
396 days	Chronic rejection with myelomatous reaction
177	Chronic rejection
99	Sepsis
78	Bronchopneumonia
21	Sepsis, Acute rejection
16	Acute rejection
Group III	
113 days	Anemia (Drug toxicity)
84	Chronic rejection
72	Chronic rejection
59	Thromboembolism
47	Acute rejection, Pneumonia
24	Anemia (Unknown)
23	Anemia (Unknown)
14	Acute rejection, Pneumonia

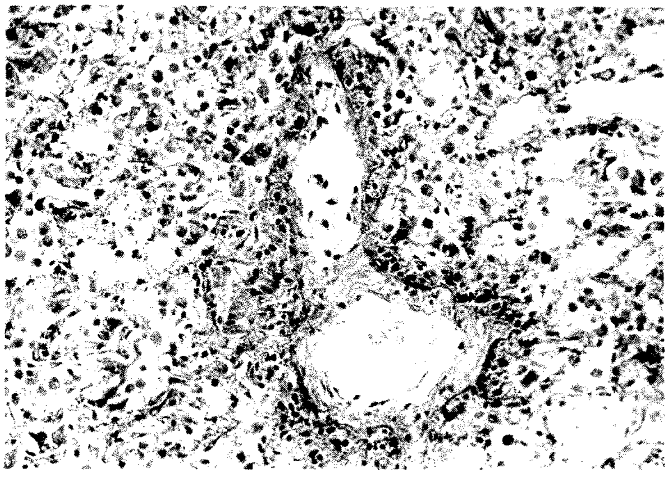


FIG. 4. Chronic rejection in a 177-day survivor; severe vascular involvement with interstitial fibrosis and alveolar obliteration (elastic tissue stain, original magnification × 66).

FIG. 5. Pulmonary arteries in the grafts showing chronic rejection. (Elastic tissue stain, original magnification × 33). A. A medium-sized pulmonary artery shows severe perivascular fibrosis, but neither fibrinoid necrosis nor obliterative intimal thickening at 72 days post-transplant. B. Small pulmonary arteries also appear devoid of intimal thickening at 396 days post-transplant.

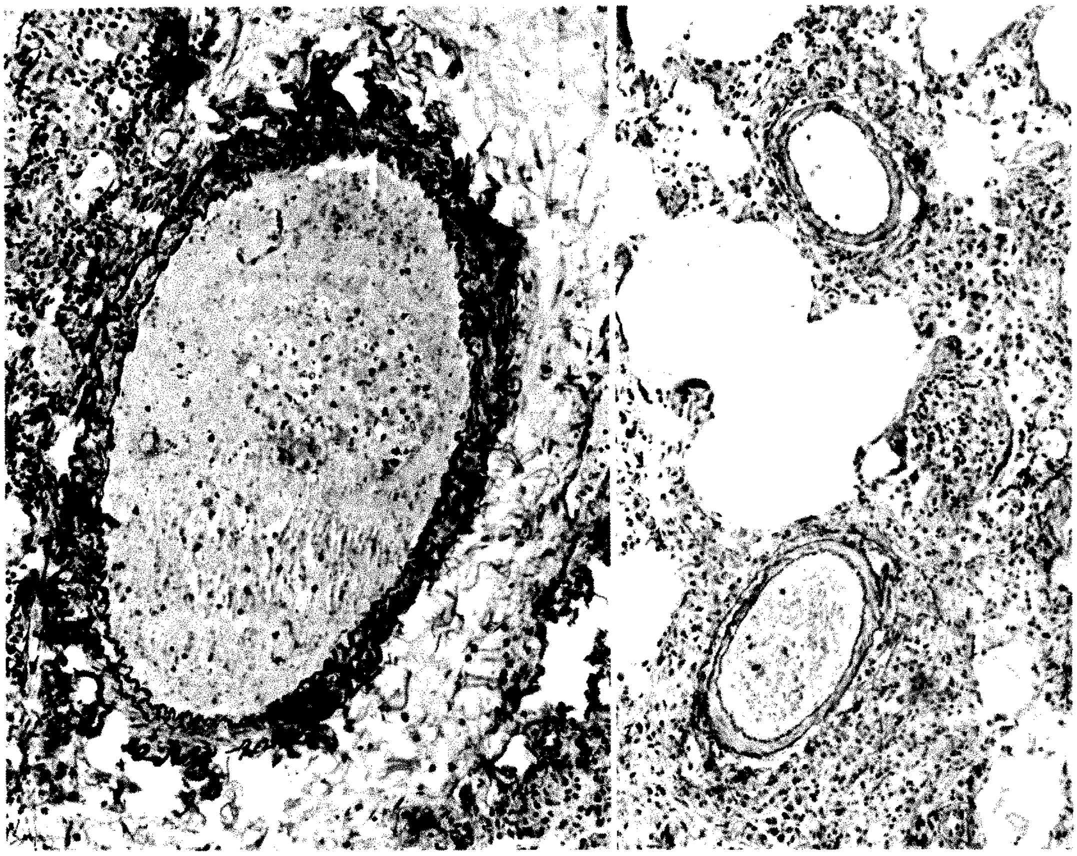
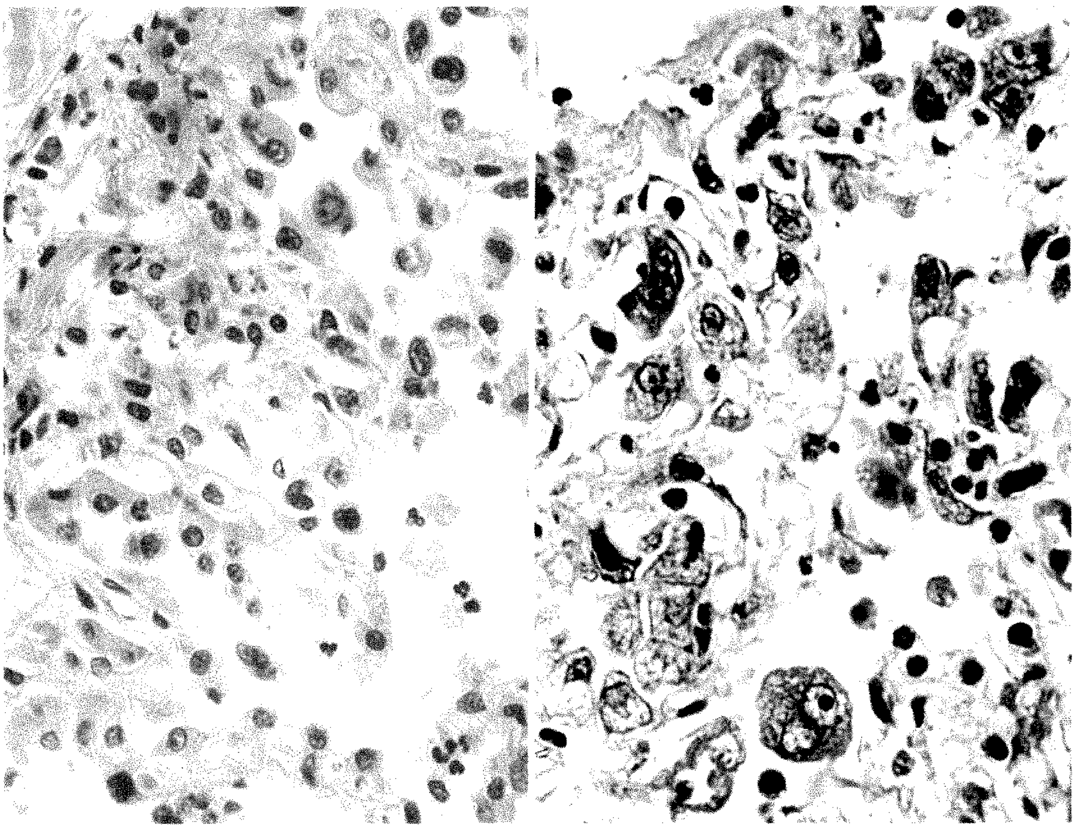


FIG. 6. Atypical pneumocytes (hematoxylin-eosin, original magnification × 133). A. In an 84-day survivor. B. In a 72-day survivor.



were so arranged as to form an alveolar lining in close contact with the alveolar capillaries (Figs. 6A, B). These cells showed no hemosiderin ingestion, suggesting a lack of phagocytic activity. They were possibly derived from type 2 pneumocytes, since our previous study in electron microscopy demonstrated many microvilli and osmiophilic lamellar bodies in their cytoplasm. Immunofluorescent study revealed no specific fluorescence of either IgG or IgM antibodies in these cells. The changes in some grafts were seen diffusely from the pleural surface to the center of the lobe, and in others the changes were mild and localized. These alterations were seen in more than half of the specimens obtained from the dogs surviving over 2 weeks. However, such evidence was not seen in the long-functioning bilateral reimplants (Fig. 7). Figure 8 schematically recollects the pathologic changes described in this paper as chronic rejection of the lung allografts.

Discussion

The histologic findings of acute rejection in bilateral lung allografts were consistent with previous descriptions by many investigators working with unilateral allografts.[1,2,4,5,8,9,12,23,24] Although the amount of graft, and consequently the amount of antigen, was doubled in the bilateral procedure, no difference in the nature of reaction was detected. It is important to emphasize, however, that the final stage of rejection reaction, as based on vital functional capacity, presents much earlier than predicted from the unilateral procedure. Hemorrhagic necrosis of the lung allograft, first described by Barnes and colleagues,[2] would be found only in the unilateral allograft; it was not demonstrated in any of our bilateral allotransplants.

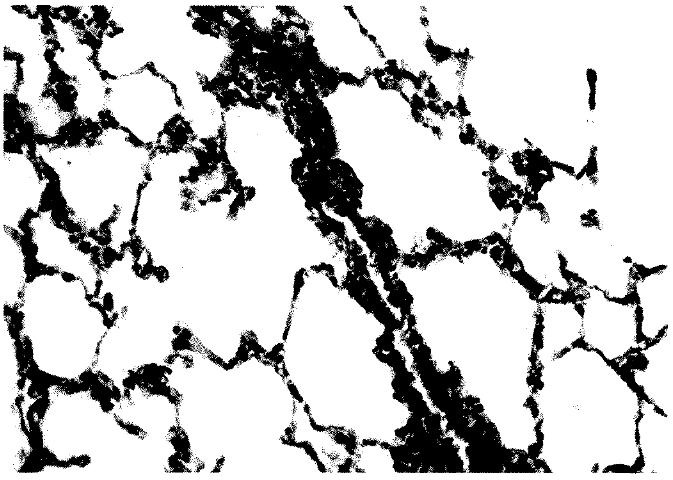


FIG. 7. Apparently normal architecture of bilateral lung reimplant, biopsied at 2 years post-transplant (hematoxylin-eosin, original magnification × 66).

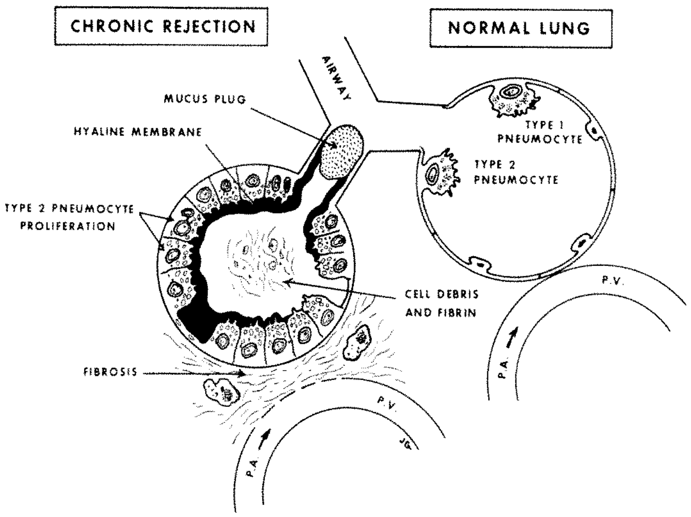


FIG. 8. Schematic drawing shows theoretical pathologic changes in chronic rejection. The normal alveoli are lined mainly by membranous type 1 pneumocytes with scattered type 2 pneumocytes, and are in close contact with the vascular system through the basement membranes. In the chronic allografts, the alveolar lining cells are frequently replaced by very atypical cells possibly derived from type 2 pneumocytes. The bronchus is occluded by mucus plugs, and the alveolar survace is covered with hyaline membrane, or obliterated by organized fibrocellular exudate. The alveolar wall is thickened by fibrosis.

As a general rule, the longer the animal survived, the greater the pathologic changes seen in the grafts. Obviously, all these changes can be interpreted as a result of repeated rejection and infection processes, since no such changes are observed in any of the bilateral reimplants.

Chronic rejection may be defined as a clinical entity observed in the recipients of organ allotransplant, in which the sequential events likely to occur in the long-functioning allograft lead to insufficiency of the organ. Therefore, we used the term to denote the condition which is observed in the final stage of the long-functioning allotransplant but not of the reimplant, thus suggesting direct or indirect participation of the immunologic process. Several characteristic features were noted. First, there was no obliterative intimal thickening in the pulmonary arteries of any size, and internal elastic lamellae did preserve their integrity. This favorable finding is in sharp contrast to that in the kidney and heart allografts, in which progressive arterial obliteration is a serious problem in long-term survivors in both man and dog.[17,22]

The second distinct feature of chronic rejection is the presence of very abnormal cells, possibly type 2 pneumocytes replacing type 1 pneumocytes on the alveolar surface. Our previous study using scanning and transmission electron microscopy also confirmed these findings.[16] An increase in the number of type 2 pneumocytes has been observed by several investigators,[3,10,19] but their findings were limited to the early changes of rejection reaction. It appears to be a nonspecific response of the alveoli to injury, because a similar lesion has been reported in such diverse situations as oxygen toxicity, high CO_2 exposure, cobalt-60 irradiation, surgical shock, and pneumonia of viral and rickettsial etiology.[7,13,20,21] However, such changes were not found in the long-term survivors of our bilateral lung reimplants.

Alveolar edema has been recognized as an important pathogenetic feature of lung allograft rejection. Veith and colleagues described a concept of the alveolar pattern of rejection in their recent manuscript.[25] Although we still lack convincing evidence to isolate this lesion specifically from the classic type of acute rejection, precipitation and organization of interstitial and intra-alveolar edema fluid must play a major role in the manifestation of deleterious changes such as hyaline membrane formation, alveolar obliteration and interstitial fibrosis. Immunologic and non-immunologic mechanisms responsible for the development of these lesions are difficult to separate, but it is clear that remnants of these lesions persist and contribute to the ultimate death of the graft.

Acknowledgment

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Increased Oxyhemoglobin Affinity After Transfusion of Stored Blood:

Evidence for Circulatory Compensation

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The effect of change in red cell 2,3-diphosphoglycerate concentration after transfusion of ACD stored blood on arteriovenous oxygen content difference, arteriovenous oxygen tension difference and oxygen consumption was assessed in 15 injured patients in Vietnam. A significant increase in the arteriovenous oxygen *tension* difference and oxygen consumption was observed at the time of low 2,3-DPG. Change in 2,3-DPG did not correlate, however, with change in either arteriovenous oxygen *content* difference or venous PO_2. This study suggests that alterations in oxyhemoglobin affinity are effectively compensated, possibly by opening capillaries to increase blood flow to tissues, by reducing the capillary-tissue oxygen gradient to maintain the rate of tissue oxygen extraction, or by increasing cardiac output.

THE ROLE of red cell 2,3-diphosphoglycerate (2,3-DPG) in determining oxyhemoglobin affinity is well established. Increased binding of oxyhemoglobin with free 2,3-DPG decreases the affinity of hemoglobin for oxygen shifting the oxygen dissociation curve to the right. Conversely, decreased binding of 2,3-DPG increases oxyhemoglobin affinity shifting the oxygen dissociation curve to the left. In 1954 Valtis and Kennedy[16] demonstrated that blood stored in acid-citrate-dextrose (ACD) solution progressively increased its affinity for oxygen. Gullbring and Strom[3] observed *in vitro* that the left shift began within one hour after ACD was added and progressed through the seventh day of storage. Increased oxyhemoglobin affinity correlated with a fall in 2,3-DPG concentrations during storage of blood in ACD solution at 4 C.

The observed increase in oxyhemoglobin affinity suggested that transfusion of stored blood would cause inefficient oxygen unloading at the tissue level. Despite numerous experimental and clinical studies, impaired oxygen delivery with increased oxyhemoglobin affinity has not been demonstrated. This study was undertaken, therefore, to determine the effect of increased oxygen binding after transfusion of stored blood on oxygen transport in seriously injured patients.

Materials and Methods

Twenty-seven previously healthy male patients ranging 18–28 years of age were studied at the 24th Evacuation Hospital in Vietnam during June, July and August 1970. All arrived with acute combat injuries and required 4–64 pints (mean 13.5 pints) of whole blood. Of the 27 soldiers, 24 were U.S., two were Thai and one was South Vietnamese. All of the patients had penetrating injuries causes by either shell fragments or high velocity missiles. Patients were studied initially within 12 hours after initial surgical treatment and transfusion. Followup studies were performed at 24 hours, 48 hours, 4 to 6 days and 7 to 9 days following transfusion.

The transfused blood was drawn in the continental United States, anticoagulated with ACD solution (NIH solution A) and stored in plastic bags. It was then transported to Vietnam via Japan having been stored at 4 C

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for 12–22 days by the time of use. Seven of the 27 patients received one to four units of fresh blood in addition to the stored blood because of bleeding problems secondary to massive transfusion.

Arterial and venous oxygen contents were calculated from direct measurements of hemoglobin concentration and hemoglobin percent saturation and from calculation of the dissolved oxygen according to the formula:

$$O_2 \text{ content} = \% \text{ sat} \times 1.34 \times \text{Hgb} + 0.0031\ PO_2$$

Anaerobic arterial and superior vena caval (SVC) blood samples were analyzed at 37 C within 15 minutes after being drawn. Hemoglobin saturation and hemoglobin concentration were determined using an Instrumentation Laboratories Co-oximeter Model 182 and pH, PO_2 and PCO_2 were determined using an Instrumentation Laboratories Model 113 Blood Gas Analyzer. The venous samples were taken from the SVC rather than the pulmonary artery because flow-directed balloon tipped catheters were not available for right heart catheterization. The position of the SVC catheters was verified radiographically and rechecked if changed, a procedure essential to the validity of using SVC venous samples in place of the mixed venous samples. SVC oxygen saturation which is normally greater than mixed venous oxygen saturation may cause significant errors when used to calculate intrapulmonary shunts. There is good correlation and no significant difference, however, between *changes* in SVC and mixed venous oxygen saturation.[10,13]

To measure oxygen consumption, expired air was collected in a rubber bag and the expiratory minute volume was measured with a Wright ventilometer through a nonrebreathing valve; the respiratory rate was recorded. Inspired gas was sampled from the respirator tubing if the patient was receiving supplemental oxygen; oxygen and carbon dioxide tensions of the inspired and expired gas samples were measured with the gas analyzer and the oxygen consumption was calculated.

Perchloric acid extracts of blood samples were neutralized, frozen and transported to the U.S. where they were analyzed for 2,3-DPG concentration by the method of Krimsky[4] as modified by Schroter and Heyden.[11] All 2,3-DPG specimens were analyzed at the same time to insure uniformity of technique.

Eleven normal non-smoking Caucasian U.S. soldiers in Vietnam served as controls for 2,3-DPG concentrations.

Results

Change in 2,3-DPG Concentration

Within 12 hours (mean sampling time 4.2 hours) after transfusion, the mean concentration of 2,3-DPG in the 27 patients studied was significantly ($p < 0.01$) below the mean of the control group (Fig. 1). Between 24 and 36 hours post-transfusion, 2,3-DPG levels increased to a level not significantly different from the control group. Two to three days post-transfusion the mean of the study group had risen further but was still within normal range. All but three of the 27 patients reached normal range by 72 hours; two of the three had received additional stored blood and the third patient reached normal on the fifth day. Four to six days posttransfusion the mean level of 2,3-DPG in the study group had risen significantly higher ($p < 0.01$) than the mean level of the control group. Thirteen of the 27 patients were studied at 7-9 days posttransfusion and their mean 2,3-DPG concentration remained significantly above the control level.

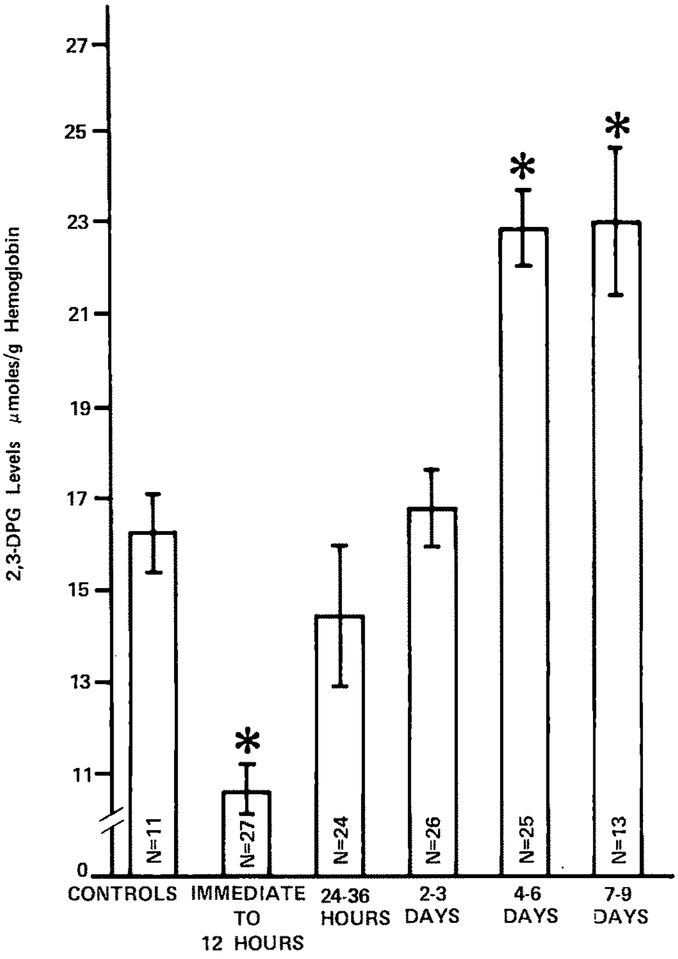

FIG. 1. Bars represent the mean (± standard error) 2,3-DPG concentration in 27 patients screened after transfusion of ACD stored blood. Asterisks represent significant ($p < 0.01$) differences from the control values.

Oxygen Transport

Fifteen of the 27 patients had depressed 2,3-DPG concentrations during the first 24 hours after transfusion and elevated concentrations 4–9 days later. To assess the effect of significant *change* in 2,3-DPG on oxygen transport, arteriovenous oxygen content difference, arterio-

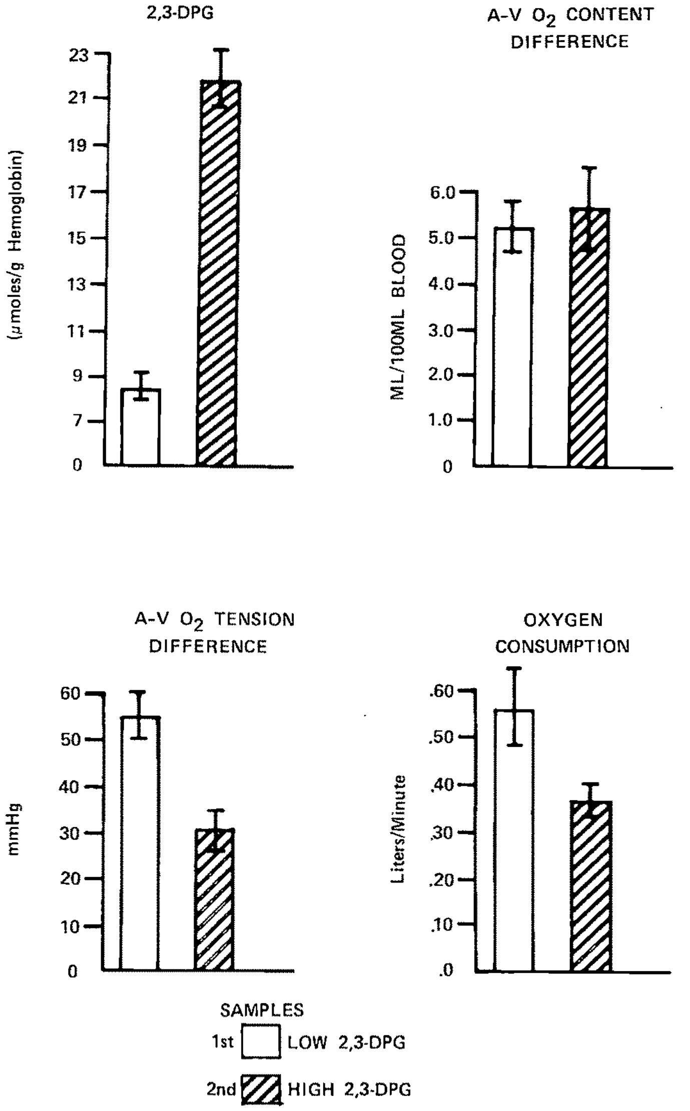

FIG. 2. Bars represent the mean (± standard error) A-V O_2 tension difference, A-V O_2 content difference and oxygen consumption at the time of low 2,3-DPG and high 2,3-DPG in the 15 patients studied. To relate the arteriovenous oxygen tension difference to oxygen content a maximum arterial PO_2 of 95 mm Hg was used to calculate the A-V O_2 tension difference in two samples.

venous oxygen tension difference and oxygen consumption were studied at the time of low (average $8.5 \pm 0.6\mu$ m/g hgb) and high (average $21.8 \pm 1.1\mu$ m/g hgb) 2,3-DPG in the 15 selected patients (Fig. 2).

No significant change in arteriovenous oxygen content difference (average 5.2 ± 0.5 ml/100 ml vs. 5.7 ± 0.9 ml/100 ml) occurred despite the marked change in red cell 2,3-DPG in the 15 selected patients. However, there was a significant ($p < 0.01$) increase in the arteriovenous oxygen tension difference (average 54 ± 6 mm hgb vs. 31 ± 5 mm hgb) at the time of low 2,3-DPG. There was no significant correlation between change in central venous PO_2 and change in 2,3-DPG.

Discussion

The transport of oxygen from the alveolus to the tissue depends upon the dynamic inter-regulation of pulmonary gas exchange, cardiac output, blood flow distribution, acid-base balance, hemoglobin concentration and the affinity of hemoglobin for oxygen. Changes in any of these transport functions may compensate, in part, for changes in the other components. The sigmoidal shape of the oxygen dissociation curve allows hemoglobin to load and unload oxygen over a narrow range of oxygen tensions, and its position, which is determined largely by the degree of binding of hemoglobin with 2,3-DPG, is critical to this function.

In vitro studies of patient's blood have shown decreased red cell 2,3-DPG and a left shift in the oxygen dissociation curve after transfusion of ACD stored blood.[2,5,14] This observation suggested that the transfusion of stored blood would cause a reduction in oxygen delivery to the tissues, particularly in patients with marginal cardiac reserve (Fig. 3). Support for this concept came from Valeri and Collins[15] who transfused stable anemic patients with washed red cells depleted of 2,3-DPG and found a transient decrease in arteriovenous oxygen content difference during the first hours after transfusion and, at the same time, no change in oxygen consumption. Calculation of cardiac indices by the Fick principle suggested that the decreased capacity of the blood to deliver oxygen was compensated by an increase in cardiac output. Miller and associates[6] postulated that a left shift in the oxygen dissociation curve would result in either a decreased arteriovenous oxygen content difference (as found in the

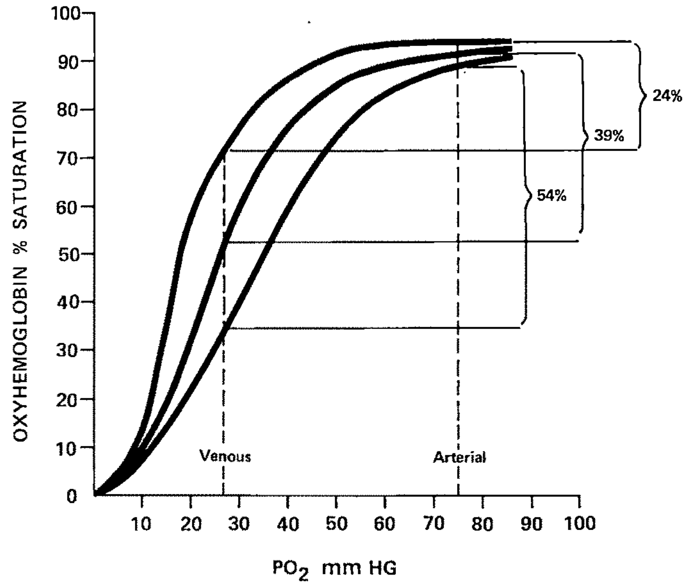

FIG. 3. Theoretical change in blood oxygen content when the oxygen dissociation curve is shifted to the left (−15%) or the right (+15%) with constant arterial and venous oxygen tensions.

early period by Valeri and Collins) or a falling venous PO_2 depending on the extent of flow compensation in the microcirculation.

In this study parameters of oxygen transport were measured to determine if, in fact, impairment of oxygen delivery occurred. Through a wide range of change in red cell 2,3-DPG concentration after transfusion the arteriovenous oxygen content difference (or the quantity of oxygen delivered to the tissues per unit volume of blood) remained unchanged. To explain this phenomenon, we examined the simultaneous changes in arteriovenous oxygen *tension* differences and found a significant increase at the time of low 2,3-DPG. This finding suggests that a constant volume of oxygen may be maintained by an increase in the arteriovenous oxygen tension difference (Fig. 4), probably as a result of a falling venous PO_2. The poor correlation found between change in 2,3-DPG and venous PO_2 is in agreement with Valeri and Collins[15] and contrary to the report by Sugerman and associates.[14] The arteriovenous oxygen *tension* difference takes into account arterial oxygen tension as a determinant of venous oxygen tension and tissue oxygenation; thus, an increase in arteriovenous oxygen tension difference (or decreased venous PO_2) reflects either 1) inadequate tissue oxygenation, 2) increased oxygen demand, or 3) compensation by the microcirculation for increased oxyhemoglobin affinity.

Since our preliminary report of this study in 1972,[1] experimental and clinical studies have appeared which support the concept that compensation for increased oxyhemoglobin affinity can occur in the microcirculation as well as through increased cardiac output. Riggs, Shafer and Guenter[9] studied changes in oxygen transport and oxygen consumption in rhesus monkeys after acute autologous exchange transfusion using 2,3-DPG depleted stored blood and found a significant decrease in the mixed venous PO_2 without evidence of acidosis, decreased oxygen consumption, or compensatory increase in cardiac output. Decrease in the venous PO_2 without evidence of impaired tissue oxygenation suggests that the fall in venous PO_2 adequately compensated for the change in oxyhemoglobin affinity without producing tissue hypoxia. Rand and associates[8] compared blood gas oxygen consumption, cardiac output, and tissue oxygenation in rabbits with high or low red cell 2,3-DPG concentrations as they were exposed to a graduated hypoxic stress. In these experiments, interestingly, there was no difference in tissue oxygenation during progressive hypoxia despite widely separated 2,3-DPG and *in vivo* p50 levels in the experimental groups. To determine the effect of increased oxyhemoglobin affinity on work performance, Woodson, Ranne and Detter,[17] after exercising trained rats to exhaustion on a graded treadmill test, found no change in work capacity after exchange transfusion with stored ACD blood as compared with work capacity after exchange transfusion with fresh heparinized blood or fresh ACD blood.

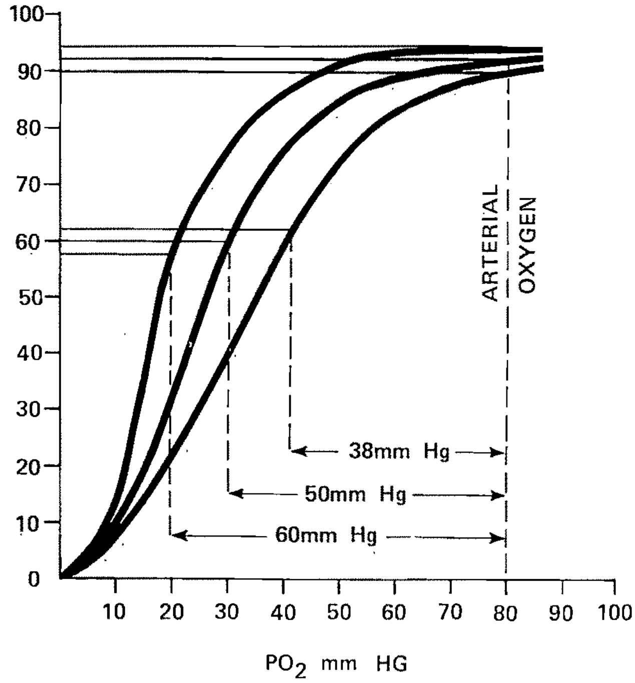

FIG. 4. Theoretical change in A-V O_2 tension difference when the oxygen dissociation curve is shifted to the left (+10 mm Hg) and right (−12 mm Hg) at a constant arteriovenous hemoglobin saturation and arterial oxygen tension.

Studying 10 hypoxic patients recovering from shock, Proctor and Fry[7] found no improvement in oxygen consumption following infusion of inosine, pyruvate and phosphate despite concomitant increase of the *in vivo* p50 values. They concluded that changes in red cell 2,3-DPG probably do not play a clinically significant role in oxygen consumption. And Shires and associates[12] reported, in a study similar to ours, no correlation between 2,3-DPG concentration and mixed venous PO_2, arteriovenous oxygen content difference and oxygen consumption.

The net oxygen extraction by the tissue may be unaffected by changes in oxygen binding if adequate compensatory flow mechanisms occur at the microcirculatory level to maintain oxygen extraction. Our data and the findings in the clinical and experimental studies discussed above suggest that the body compensates for alterations in oxyhemoglobin binding by either increased cardiac output, modulations of oxygen extraction in the tissue across a decreased capillary-tissue gradient or by alterations in microcirculatory blood flow. Although we did not find demonstrable impairment of oxygen transport after massive transfusion, these findings, which reflect the sum of changes occurring across multiple organ systems, must be viewed with reservation until a reliable technique for determining tissue oxygenation is developed. Compensatory decrease in venous PO_2 (or increase in arteriovenous oxygen tension difference) may be harmful if a decreased capillary-tissue oxygen gradient, inadequate for tissue oxygen delivery, occurs in essential organs. Nevertheless, present evidence suggests that changes in oxyhemoglobin affinity are of minor importance in determining tissue oxygenation. Consideration of altered oxygen binding after blood storage should not mitigate against the use of stored blood until more precise information is available.

Acknowledgments

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Effect of Malnutrition on Colonic Healing

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It has been suggested that colonic healing is impaired in malnourished subjects, but there have been no biochemical studies of the effect of malnutrition on colonic healing. The effects of malnutrition on the colon and the healing of colonic anastomoses were studied in rats fed a protein-free diet. Test animals were compared with control animals of similar age, and control animals of similar weight. There was a significant reduction in the body weight, total serum proteins and serum albumin of animals starved of protein. Malnutrition resulted in a reduction in the weight of the uninjured colon, and an increase in the colonic collagen *concentration*. There was a significant reduction in the collagen *content* of the colon in animals starved of protein for seven weeks, and the collagen *content* of anastomoses in these animals was significantly lower than the value in control animals. Anastomotic edema occurred during colon healing in animals starved for seven weeks. Measurements of colonic bursting pressure were an inaccurate guide to colonic healing. It is concluded that severe malnutrition resulting in 34% loss of body weight had an adverse effect on colonic healing.

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CLINICAL AND EXPERIMENTAL STUDIES have shown that malnutrition has an adverse effect on the healing of wounds of skin and abdominal fascia.[16,17,21,22] Tissue collagen is removed during malnutrition,[2,3,10] and studies of experimental wounds have shown that collagen synthesis is defective in malnourished subjects.[21,24,27]

Clinical observations have suggested that the healing of colonic anastomoses may be affected by malnutrition,[12] and recent experimental investigations seem to support this contention. It has been shown that the tensile strength of healing colonic wounds and anastomoses is abnormally low in malnourished rats.[4,5,18] However, precise information regarding the biochemical features of colonic healing in malnourished subjects is lacking.

In this study, the effects of malnutrition on the colon and healing colonic anastomoses were studied in rats.

Methods

Two-hundred and sixty male Sprague Dawley rats were studied. Control animals were fed a normal rat diet, and test animals received a protein-free diet. The composition of test and control diets was based on the recommendations of Hegstead and Chang[11] (FIG. 1). The normal rat diet contained 25% casein, and the caloric deficit in the protein-free test diet was corrected by increasing the amount of cornstarch. However, it was observed that rats consumed the test diet less avidly than the control diet, and it is likely that test animals were subjected to protein-calorie malnutrition rather than simple starvation of protein.

Test animals weighed 220–270 gm at the start of the experiment, and they were later compared with control animals of similar age (age controls), and control animals of similar weight (weight controls).

Serum Proteins

Blood was withdrawn by cardiac puncture for the measurement of serum proteins. Total protein was determined by the biuret method, using the standard Technicon autoanalytic procedure, and the serum globulin was measured by the glyoxylic-tryptophan reaction.[8] The serum albumin was determined from the difference between the total protein and globulin values.

Uninjured Colon

Standard biopsies of the left colon measuring 5 mm in width were obtained from test and control animals. The wet weights of the biopsies were determined, and the specimens were dried to constant weight in an oven at 106 C. The biopsies were hydrolyzed in 6N hydro-

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CONTROL AND PROTEIN-FREE DIETS
after Hegstead and Chang. J. NUTRITION 85, 159, 1965

DIETARY CONSTITUENTS	CONTROL (NORMAL) RAT DIET (% of Total Weight)	PROTEIN-FREE (TEST) DIET (% of Total Weight)
CASEIN	25·0	—
CORNSTARCH	60·0	85·0
HYDROGENATED COTTONSEED OIL	8·0	8·0
HAWK-OSER SALT MIXTURE	4·0	4·0
VITAMIN SUPPLEMENT	1·0	1·0
CELLULOSE NON-NUTRITIVE FIBRE	2·0	2·0

FIG. 1. Constituents of test and control diets.

chloric acid, and the collagen content was determined by the measurement of hydroxyproline, using the auto-analytic procedure of Jackson and Cleary.[13]

Age controls, weight controls, and test animals were sacrificed for measurements of colonic tensile strength. Segments of the left colon measuring 8 cm in length were resected, and the colonic bursting *pressure* was determined with a mercury manometer during distention of the colon with air at a constant rate of 1 ml/minute. The colonic bursting *wall tension* was determined from the product of the bursting pressure and the radius of the bowel at the point of rupture, according to the Law of La Place.[19]

Colonic Anastomoses

The healing of colonic anastomoses was studied in age controls, weight controls, and test animals in groups of 16–20. Segments of bowel measuring 1 cm long were resected from the distal left colon, and end-to-end anastomoses were made with an inverting technique, using a single layer of interrupted 6-0 silk sutures. The animals were sacrificed immediately or on the third or seventh postoperative days, and the tensile strength and collagen content of the anastomoses were determined as described above. The anastomoses were completely excised as standard strips of tissue measuring 5 mm in width, and the total collagen content was determined.

Statistical analyses of the results were made, using the Student t-test.[7]

Results

Body Weight

The weight changes in test animals and age controls are shown in Fig. 2. Two groups of age controls, each comprising 20 animals, were studied for three weeks prior to surgery. These animals increased their weight by 34% during this period. Three groups of test animals, each comprising 20 animals were subjected to protein starvation lasting three, five and seven weeks. Animals starved for three weeks lost 25% of their body weight; weight loss after five weeks of starvation was 27%; and protein starvation for seven weeks resulted in a weight loss of 34%.

Two groups of weight controls were studied, and the weights of these animals were similar to those of test animals starved for five and seven weeks. The average body weight of one group of 20 weight controls was 164 gm (S.E. ± 2.21), and the average weight of the other group of 16 animals was 185 gm (S.E. ± 2.20).

Serum Proteins

Table 1 shows the mean values for total serum protein and serum albumin in age controls, two groups of weight controls, and six groups of test animals starved for two to seven weeks. Each group comprised seven animals. The total protein and albumin values in test animals starved for two weeks were significantly lower than the values in age controls (for total protein, $P < 0.01$; for albumin, $P < 0.001$), and the serum proteins decreased as starvation progressed.

In the weight controls, the serum protein values in the group with an average weight of 185 gm were not

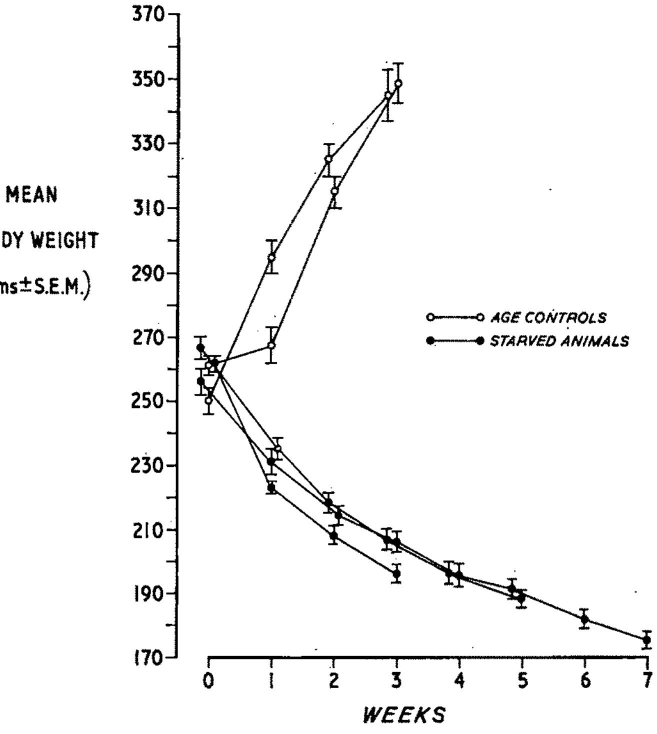

FIG. 2. Body weight measurements in age controls and three groups of test animals starved for three, five and seven weeks.

TABLE 1. *Total Serum Protein and Serum Albumin Measurements in Age Controls, Two Groups of Weight Controls, and Groups of Test Animals Starved for Two to Seven Weeks*

Animals	Mean Total Serum Protein (g/100 ml ± S.E.)	Mean Serum Albumin (g/100 ml ± S.E.)
Age Controls	6.61 ± 0.11	3.58 ± 0.08
Weight Controls (Mean Body Weight 164 g)	5.62 ± 0.07	3.28 ± 0.08
Weight Controls (Mean Body Weight 185 g)	6.35 ± 0.17	3.42 ± 0.10
Two Weeks Starvation	6.18 ± 0.12	2.92 ± 0.09
Three Weeks Starvation	5.74 ± 0.15	3.02 ± 0.07
Four Weeks Starvation	5.65 ± 0.10	2.84 ± 0.05
Five Weeks Starvation	5.46 ± 0.26	2.66 ± 0.18
Six Weeks Starvation	5.30 ± 0.05	2.57 ± 0.05
Seven Weeks Starvation	4.94 ± 0.27	2.28 ± 0.15

significantly different from those of age controls, but the values in the group with an average weight of 164 gm were significantly lower than those of age controls (for total protein, $P < 0.001$; for albumin, $P < 0.02$). However, the proteins in the latter group of weight controls were significantly higher than those of test animals starved for seven weeks (for total protein, $P < 0.05$; for albumin, $P < 0.001$).

Uninjured Colon

Table 2 shows the mean values for the wet weight, percentage of water content, total collagen content, and collagen concentration in standard biopsies of colon from age controls, the two groups of weight controls, and groups of test animals starved for three, five and seven weeks. Nineteen age controls were studied, and the two groups of weight controls comprised 16 and 20 animals. The groups of test animals starved for three, five and seven weeks comprised 18, 20 and 16 animals respectively.

The wet weights of colon biopsies from starved animals were significantly lower than those of age controls ($P < 0.005$) and weight controls ($P < 0.001$), but the relative water content of the biopsies from starved animals was significantly greater than that of age controls ($P < 0.001$). However, the relative water content of biopsies from weight controls was significantly greater than that of age controls and test animals ($P < 0.01$).

The total collagen content of colon biopsies from test animals was not significantly different from that of age controls except in the case of the test group starved for seven weeks. In this group, the total collagen content was significantly lower than the value in age controls ($P < 0.02$). The total collagen content of biopsies from weight controls was significantly lower than that of test animals and age controls ($P < 0.001$).

The collagen concentration in dry colonic tissue in test animals was significantly higher than the values in age controls and weight controls ($P < 0.01$), but there was no difference between the values in age controls and weight controls.

The collagen concentration in wet colonic tissue in test animals starved for three and five weeks was significantly higher than the value in age controls ($P < 0.005$), but there was a sharp decline in this parameter in animals starved for seven weeks. The striking feature, however, was the value in weight controls. In these animals, the collagen concentration in wet tissue was less than 50% of the value in age controls and test animals.

The tensile strength measurements in the uninjured colon of age controls, weight controls, and test animals starved for two to seven weeks are shown in Table 3. Each group comprised five animals. There was a progressive rise in the colonic bursting *pressure* in test animals as starvation progressed, and the bursting pressures in test animals and weight controls were higher than the values in age controls. However, the bursting *wall tension* results showed a different trend. The colonic bursting wall tension declined progressively in test animals as the duration of starvation increased, and the results in test animals starved for six and seven weeks were significantly lower than the value of age controls ($P < 0.05$). The results in test animals starved for seven weeks were also

TABLE 2. *Uninjured Colon: The Wet Weight, Percentage Water Content, Total Collagen Content, and Collagen Concentration in Standard Biopsies of Colon From Age Controls, Two Groups of Weight Controls, and Three Groups of Test Animals Starved for Three, Five and Seven Weeks*

Animals	Mean Wet Weight (mg ± S.E.)	Mean Water Content (% ± S.E.)	Mean Total Collagen Content (ug ± S.E.)	Mean Collagen Concentration in Dry Tissue (ug/mg ± S.E.)	Mean Collagen Concentration in Wet Tissue (ug/mg ± S.E.)
Age Controls	17.8 ± 0.61	85.7 ± 0.80	389 ± 15.29	179.6 ± 9.64	22.4 ± 1.12
Weight Controls (Mean Body Weight 164 g)	20.3 ± 0.97	93.6 ± 0.46	228 ± 7.91	186.9 ± 12.01	11.0 ± 0.44
Weight Controls (Mean Body Weight 185 g)	21.1 ± 1.12	92.8 ± 0.44	242 ± 13.26	165.8 ± 5.37	11.7 ± 0.54
Three Weeks Starvation	14.7 ± 0.67	89.4 ± 0.56	394 ± 14.22	267.4 ± 15.39	27.1 ± 0.83
Five Weeks Starvation	15.0 ± 0.55	89.4 ± 0.60	438 ± 21.74	292.9 ± 19.69	29.5 ± 1.37
Seven Weeks Starvation	14.5 ± 0.70	89.4 ± 1.11	338 ± 12.84	274.4 ± 35.73	23.6 ± 0.56

TABLE 3. *Uninjured Colon: Tensile Strength Measurements in Age Controls, Two Groups of Weight Controls, and Groups of Test Animals Starved for Two to Seven Weeks*

Animals	Mean Colonic Bursting Pressure (mm Hg ± S.E.)	Mean Colonic Bursting Wall Tension (Dynes/cm × 10^{-5} ± S.E.)
Age Controls	179 ± 13.82	0.725 ± 0.038
Weight Controls (Mean Body Weight 164 g)	230 ± 3.20	0.782 ± 0.043
Weight Controls (Mean Body Weight 185 g)	210 ± 8.94	0.761 ± 0.026
Two Weeks Starvation	192 ± 5.83	0.672 ± 0.049
Three Weeks Starvation	195 ± 8.00	0.649 ± 0.074
Four Weeks Starvation	185 ± 7.07	0.578 ± 0.073
Five Weeks Starvation	208 ± 9.80	0.642 ± 0.018
Six Weeks Starvation	208 ± 8.60	0.573 ± 0.042
Seven Weeks Starvation	211 ± 3.65	0.589 ± 0.043

significantly lower than the values in weight controls ($P < 0.01$), but there was no difference between the results in age controls and weight controls.

Colonic Anastomoses

Figure 3 shows the results of colonic tensile strength measurements on the third and seventh postoperative days in age controls and test animals starved for three, five and seven weeks. Each of the four groups comprised 20 animals, and equal numbers of animals were sacrificed on the third and seventh postoperative days.

The bursting *pressure* and bursting *wall tension* showed a similar trend. There was no difference between the results in age controls and test animals starved for three or five weeks, but the tensile strength of anastomoses in test animals starved for seven weeks was significantly lower than the value in age controls on the seventh postoperative day ($P < 0.005$).

Tensile strength measurements in age controls, two groups of weight controls, and the test group starved for seven weeks are shown in Fig. 4. The two groups of weight controls comprised 20 and 16 animals, and equal numbers of animals were sacrificed on the third and seventh postoperative day.

Again, the colonic bursting *pressure* and bursting *wall tension* results showed a similar trend. The results in the group of weight controls with an average weight of 185 gm were not significantly different from those of age controls, but the results in the group of weight controls with an average weight of 164 gm were significantly lower than the values in age controls ($P < 0.02$). The results in this group of weight controls were rather similar to those of test animals starved for seven weeks.

Figure 5 shows the total collagen content of the anastomoses on the third and seventh postoperative days in age controls and the groups of test animals starved for three, five, and seven weeks. The results in test animals starved for three weeks were not significantly different from those of age controls. The collagen content of anastomoses in test animals starved for five and seven weeks was significantly lower than that of age controls on the third postoperative day ($P < 0.001$), and the collagen content of anastomoses in the group starved for seven weeks was also significantly lower than the value in age controls on the seventh postoperative day ($P < 0.005$). The results in test animals starved for five weeks were not significantly different from those of control animals on the seventh day.

The total collagen content of anastomoses in the two groups of weight controls, age controls, and test animals starved for seven weeks is shown in Fig. 6. The collagen content of anastomoses removed on the day of surgery from six age controls, eight test animals, and six weight controls weighing an average of 164 gm is also shown.

The total collagen content of anastomoses in weight controls and test animals was significantly lower than the value in age controls on the day of surgery, and this

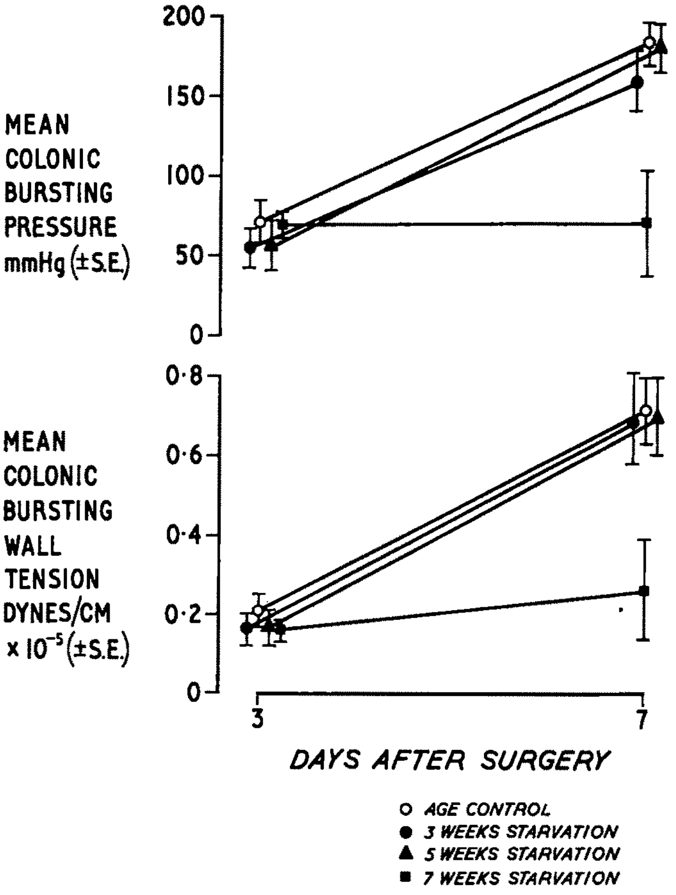

FIG. 3. Colonic anastomoses. Tensile strength measurements in age controls and groups of test animals starved for three, five, and seven weeks. Each group comprised 20 animals, and equal numbers of animals were sacrificed on the third and seventh postoperative days.

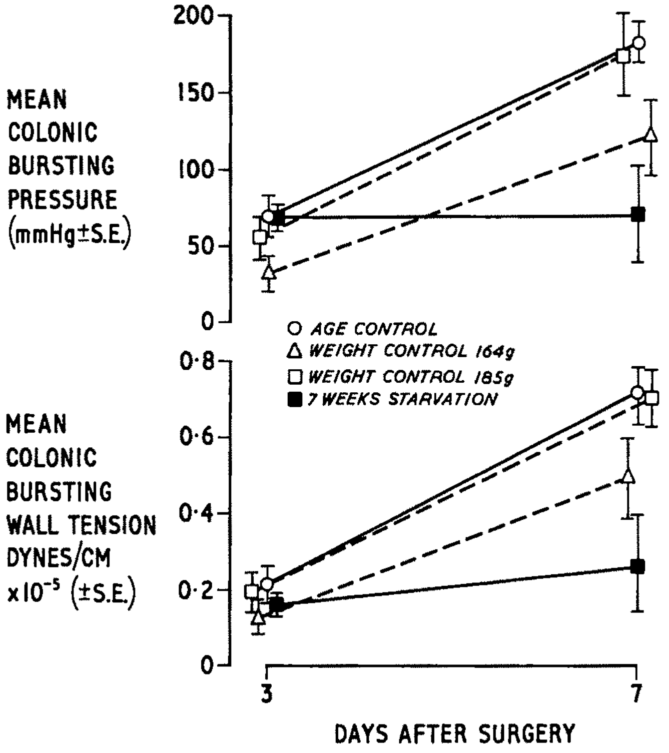

FIG. 4. Colonic anastomoses. Tensile strength measurements in age controls, two groups of weight controls, and the group of test animals starved for seven weeks.

difference was also apparent on the third postoperative day. However, active collagen synthesis occurred in the anastomoses in age controls and weight controls after the third day, and the collagen content of anastomoses in weight controls and age controls was significantly higher than that of test animals on the seventh postoperative day ($P < 0.005$).

Figure 7 shows the collagen concentration in anastomoses in age controls and the three groups of test animals starved for three, five and seven weeks.

The results do not show a close correlation with the total collagen measurements since the colonic collagen concentration in starved animals is abnormally high. However, there was a striking difference between the collagen concentration in wet and dry tissue in test animals starved for seven weeks. In this group, the collagen concentration in dry tissue increased between the third and seventh postoperative days, but there was a striking reduction in the collagen concentration in wet tissue during this period, indicating that a significant degree of edema complicated anastomotic healing in these animals.

Discussion

The biochemical factors which affect wounds in malnourished subjects may be quite complex, but defective collagen synthesis appears to be the major abnormality.[21,24,25] However, little is known of the effects of malnutrition on visceral healing. Studies in experimental animals have shown that visceral collagen is removed to a lesser extent than skin collagen in malnourished subjects,[3,10] but it is not known if visceral wound healing is less affected by malnutrition than the healing of skin wounds.

Mukerjee and colleagues[18] reported that the tensile strength of colonic wounds in malnourished rats was inferior to that of control animals, but these observations must be interpreted with caution since questionable assumptions were made in the measurement of colonic tensile strength. Daly and associates[4,5] found that there was a striking reduction in the tensile strength of colonic anastomoses in rats fed a protein-free diet, and changes were apparent even when the loss of body weight amounted to only 2%.

In the present study, colon healing was studied in rats fed a protein-free diet. It became evident that the animals responded to this diet by reducing their dietary intake, and it is likely that protein-calorie malnutrition resulted. Similar observations in animals given protein-free diets have been described previously.[23]

Malnutrition resulted in progressive loss of body weight and a reduction in the serum proteins. Changes in the serum proteins were found in test animals after two weeks of protein starvation, and the reduction in body weight and proteins was accompanied by changes in the colon. There was a reduction in colonic weight, and an increase in the colonic collagen concentration, indicating that non-collagenous materials were removed from the colon of starved animals. It seems likely that the removal of non-collagenous proteins and fat accounted for the

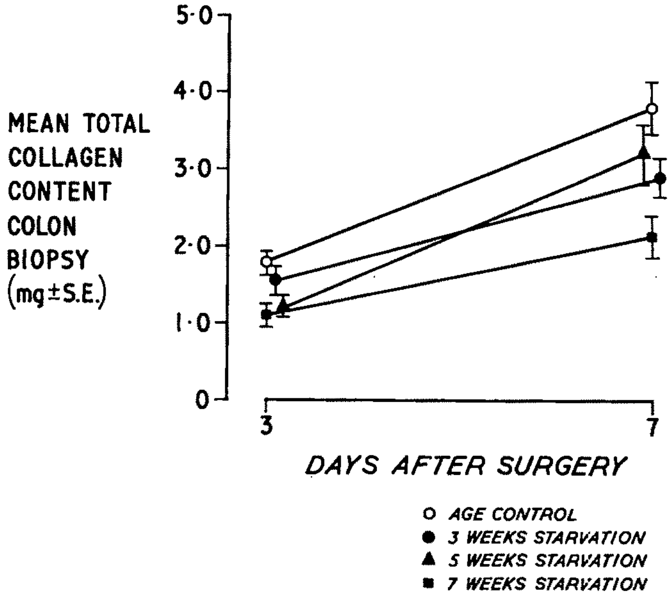

FIG. 5. Colonic anastomoses. The total collagen content of anastomoses in age controls and the groups of test animals starved for three, five, and seven weeks.

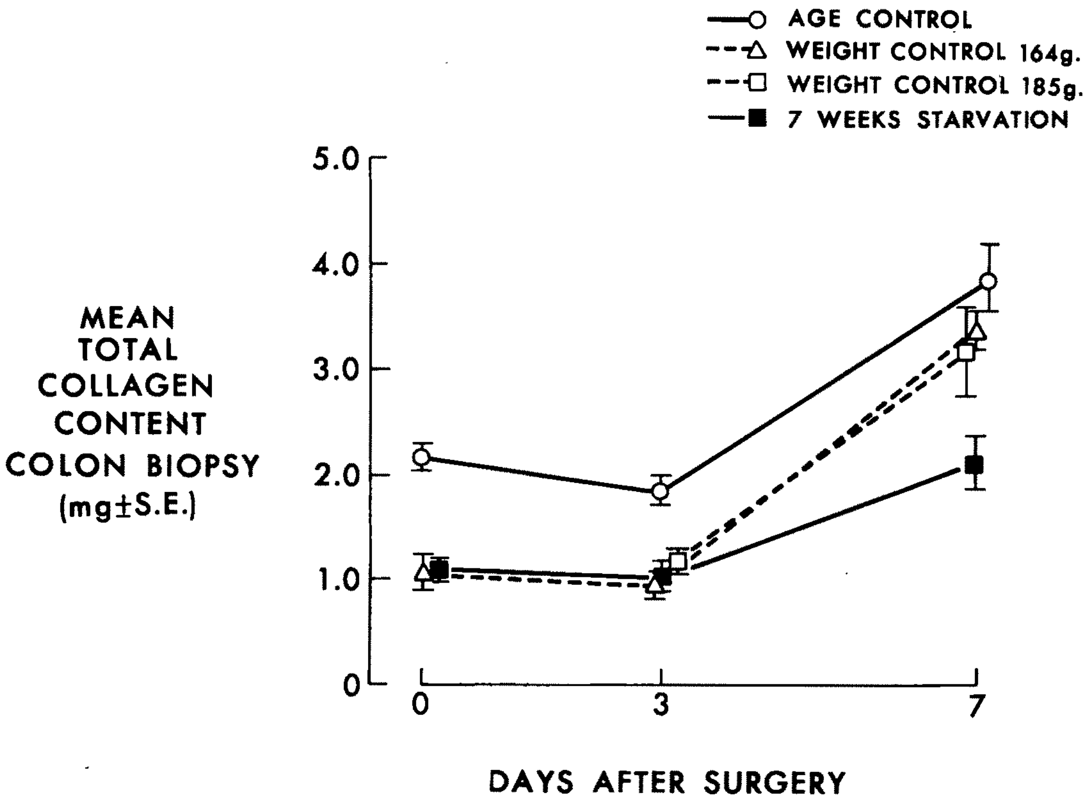

FIG. 6. Colonic anastomoses. The total collagen content of anastomoses in age controls, the two groups of weight controls, and the group of test animals starved for seven weeks. Anastomoses were removed on the day of surgery from six age controls, six weight controls, and eight test animals.

reduction in colonic weight, and these changes in the colon were accompanied by a relative increase in the colonic water content. There was little evidence of breakdown and removal of colonic collagen until the animals had been starved for seven weeks, and the loss of body weight amounted to 34%.

Test animals were compared with control animals of similar age (age controls), and control animals of similar weight (weight controls). The young weight controls differed from age controls in that they had significantly lower serum proteins, and this difference was quite striking in the case of the total protein values. According to Dimopoullos,[6] these differences between young and old animals are normal physiological features in the rat. There was also a striking difference in the collagen concentration in wet colonic tissue in age controls and weight controls due to the increased water content of the colon in young control animals. Similar differences in the collagen concentration in wet tissues in young and old rats have been described previously by Zika and Klein.[30]

The biochemical changes in the uninjured colon of starved animals were accompanied by a reduction in colonic tensile strength. This was not reflected by changes in the colonic bursting *pressure*, but this measurement is profoundly affected by the internal radius of the bowel,[10] and the radius of the colon in test animals was much less than that of control animals of similar age. The colonic bursting *wall tension*, or pressure-radius product, was a more accurate measure of colonic tensile strength in starved animals, and this parameter was significantly reduced in animals starved of protein for six or seven weeks.

Malnutrition affected the healing of colonic anastomoses only in animals starved of protein for seven weeks. These animals lost 34% of their body weight, and the tensile strength and collagen content of colonic anastomoses were significantly lower than the values in control animals. Measurements of the colonic collagen concentration in starved animals revealed the presence of edema in colonic anastomoses on the seventh postoperative day. To some extent, edema may be a normal feature of wound healing,[1] but Thompson and colleagues[25] reported that excessive edema occurred in abdominal wounds in malnourished animals. According to Thompson,[26] wound edema in malnourished subjects can be prevented by correction of the plasma colloid osmotic pressure. Daly[4,5] found no evidence of edema in colonic anastomoses in rats deprived of protein for six weeks, but his assessment was based purely on histological observations.

Clinicians have found that significant morbidity occurs in malnourished patients when weight loss exceeds 30%,[14,15] and the findings in the present study suggest that severe malnutrition has a deleterious effect on colonic healing. Daly and colleagues[4,5] found that colon healing in rats was affected by brief periods of protein deprivation, but

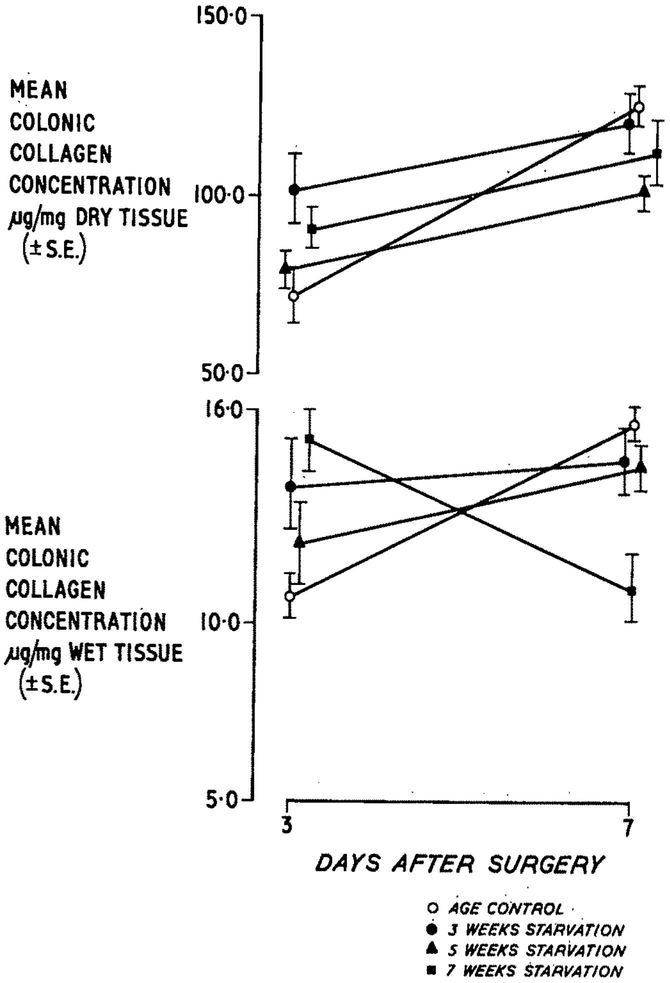

FIG. 7. Colonic anastomoses. The collagen concentration in anastomoses in age controls, and the groups of test animals starved for three, five, and seven weeks.

this assertion was based on measurements of colonic bursting pressure and the present study has indicated that measurements of colonic bursting pressure in malnourished rats may be misleading. The colon of starved animals was significantly smaller than that of control animals of similar age, and the size of the colon in starved animals resembled that of younger control animals of similar weight. The tensile strength of colonic anastomoses in these younger control animals was similar to that of starved animals, despite the presence of normal collagen synthesis in the anastomoses of control animals. It seems likely, therefore, that technical factors involved in the anastomosis of the small colon of starved rats or control animals of similar weight may result in misleading measurements of colonic tensile strength.

Clinical studies have shown that malnourished patients have an increased incidence of anastomotic dehiscence after colon surgery.[12] Various uncontrolled clinical observations[9,28,29] have suggested that improvement of the nutritional status of malnourished patients may have a favourable effect on intestinal healing, and the results of the present study imply that some form of nutritional support may be justified in severely malnourished patients undergoing colonic anastomosis.

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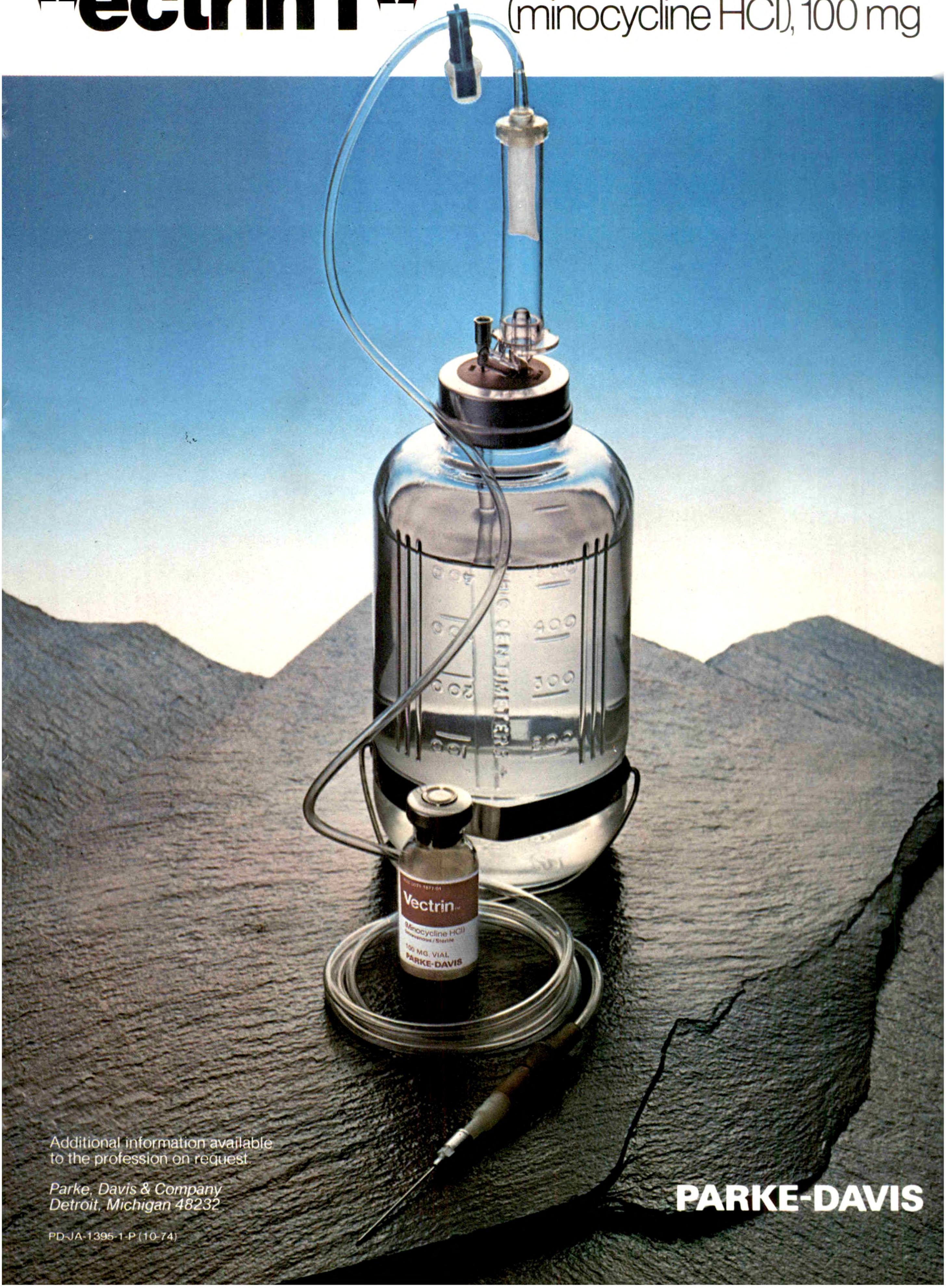

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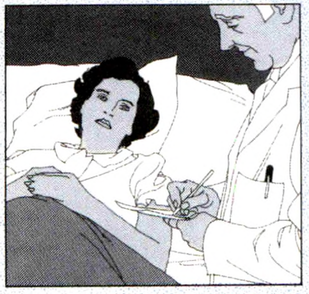

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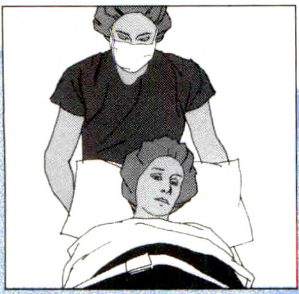
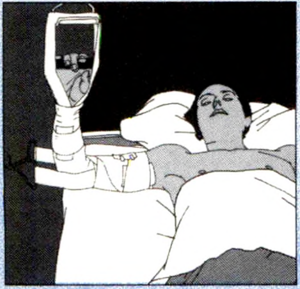


Injectable Valium (diazepam) adjunctively prior to surgery or endoscopic procedures can relieve acute anxiety and diminish recall

Although the strange surroundings and impending surgical or endoscopic procedures have been described and explained, they may still produce acute anxiety in some patients. Injectable Valium (I.M. preferred for surgery and I.V. for endoscopy) can calm the patient promptly while increasing his cooperation and acceptance of the procedure. Also, Valium frequently diminishes patient recall of the unpleasant endoscopic procedure – an important consideration if a repeat examination is necessary.

Injectable Valium seldom significantly alters vital signs, but resuscitative facilities should be available since there have been occasional reports of apnea and cardiac arrest. These have occurred particularly in the elderly, in very ill patients or those with limited pulmonary reserve; therefore, lower doses – usually 2 to 5 mg – should be used for this group.



Valium (diazepam) is useful in orthopedic surgery and can help break the cycle of spasm/pain/spasm of skeletal muscle spasm when associated with local pathology or trauma

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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome. *Oral form* may be used adjunctively in convulsive disorders, but not as sole therapy. *Injectable form* may also be used adjunctively in: status epilepticus; severe recurrent seizures; tetanus; anxiety, tension or acute stress reactions prior to endoscopic and surgical procedures; cardioversion.

Contraindications: Use of Injectable in infants and Tablets in children under 6 months of age; known hypersensitivity to drug; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, nursing women or in women of childbearing potential requires that expected benefit be weighed against possible hazard.

ORAL: Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; resuscitative facilities should be available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓ and administer in small increments. Not recommended for OB use until additional information is available. Should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects —particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available; hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis and phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Dosage: Individualized for maximum beneficial effect.

ORAL—*Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg *b.i.d.* to *q.i.d.*; acute alcohol withdrawal, 10 mg *t.i.d.* or *q.i.d.* in first 24 hours, then 5 mg *t.i.d.* or *q.i.d.* as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg *t.i.d.* or *q.i.d.*; adjunctively in convulsive disorders, 2 to 10 mg *b.i.d.* to *q.i.d.* *Geriatric or debilitated patients:* 2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg *t.i.d.* or *q.i.d.* initially, increasing as needed and tolerated (not for use under 6 months).

INJECTABLE: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Immediate gastric lavage indicated for overdosage with tablets. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

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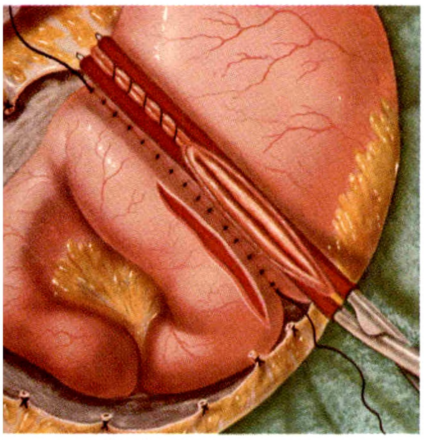
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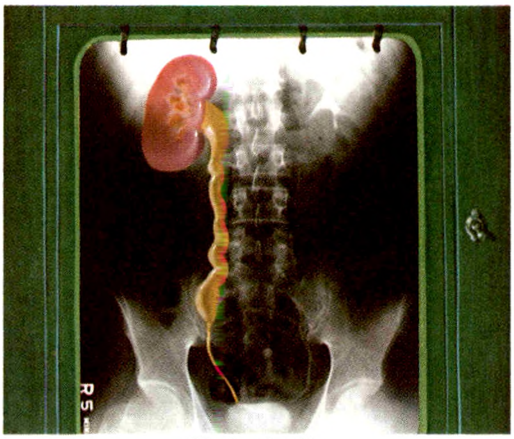
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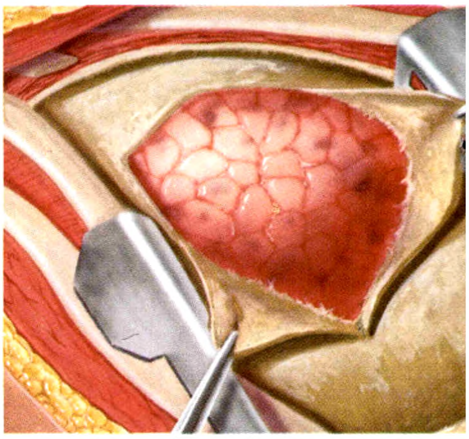
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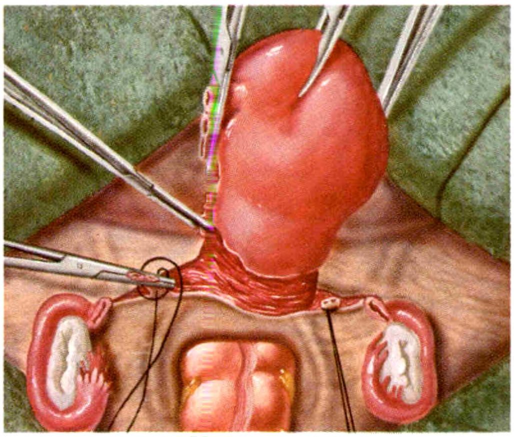
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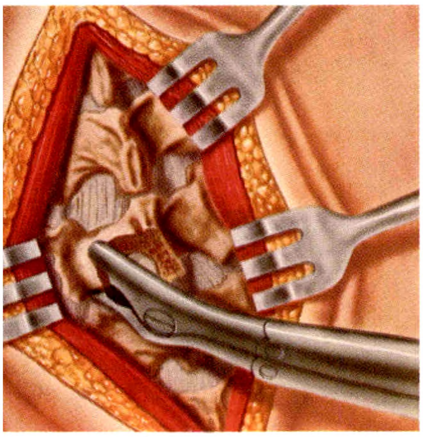
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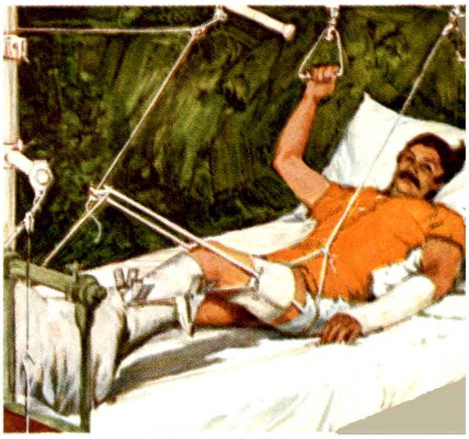
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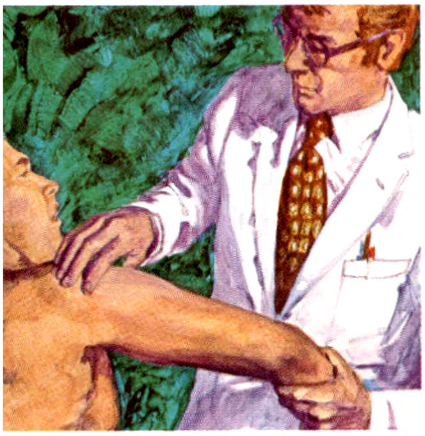
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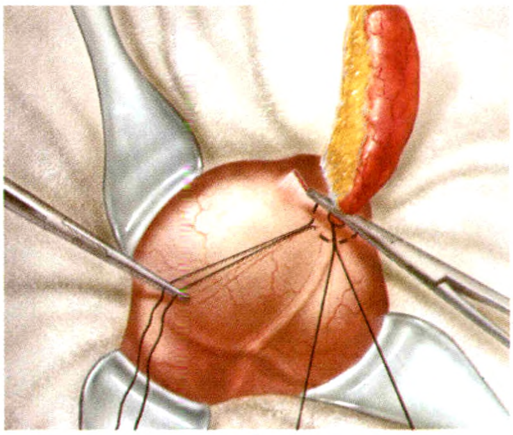
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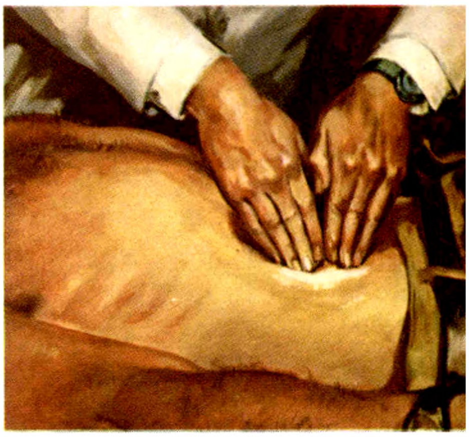

Intestinal colic

Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

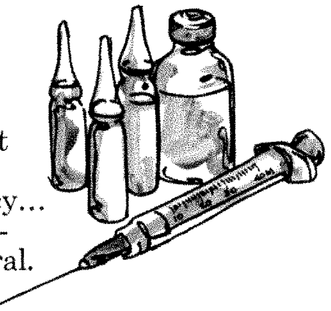
the unextreme injectable for serious pain

Talwin doesn't go to extremes.

Yet, Talwin relieves serious pain (moderate to severe pain) in the great majority of everyday hospital situations.

For most serious pain—Talwin has in fact been shown comparable to narcotics such as morphine and meperidine, in analgesic efficacy... with less likelihood of some of the extreme adverse effects produced by the opiates in general.

With Talwin there is a low incidence of respiratory depression, hypotension, urinary retention, and constipation.



In moderate to severe pain

Injectable **Talwin**®
brand of
pentazocine
(as lactate)

extremely effective for most patients

30 mg. 45 mg. 60 mg.

See important product information concerning warnings, adverse reactions, patient selection, prescribing and precautionary recommendations on last page of this advertisement.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp™—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for Injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

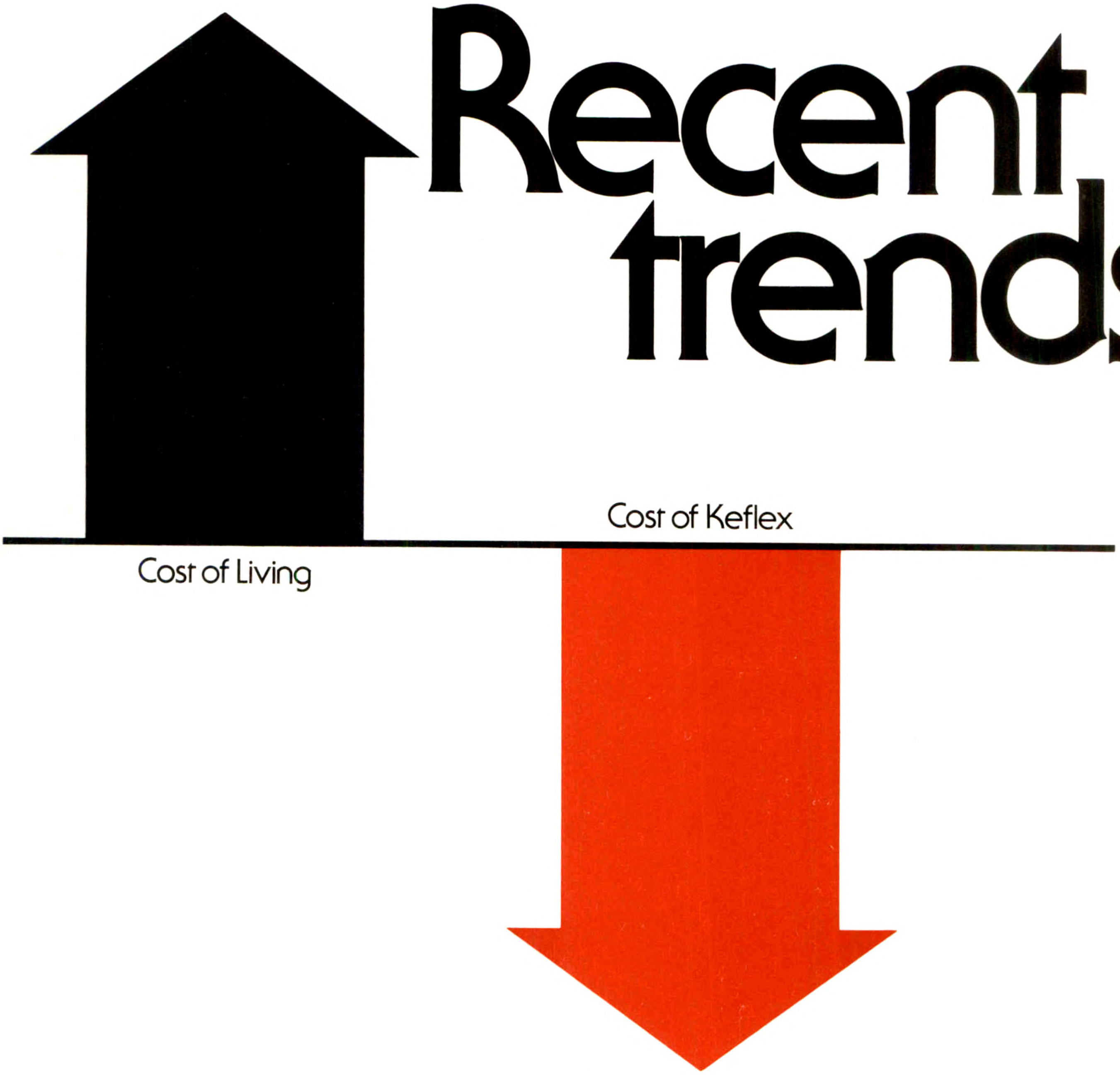
Winthrop

(1639M)

the unextreme injectable for serious pain

Injectable
Talwin®
brand of
pentazocine
(as lactate)

Recent trends



Eli Lilly and Company is pleased to announce that the price of Keflex has been reduced for the third time in three years. This means that Keflex now costs 21 to 35%* less than it did when introduced in 1971.

*Based on price reductions by Eli Lilly and Company to distributors in 1972, 1973, and 1974. Percentage of reduction varies according to dosage form, strength, and package size. A 250-mg.† Pulvule of Keflex in a bottle of 100 now costs 32% less than when it was first introduced in 1971 in bottles of 24.

†Equivalent to cephalexin.

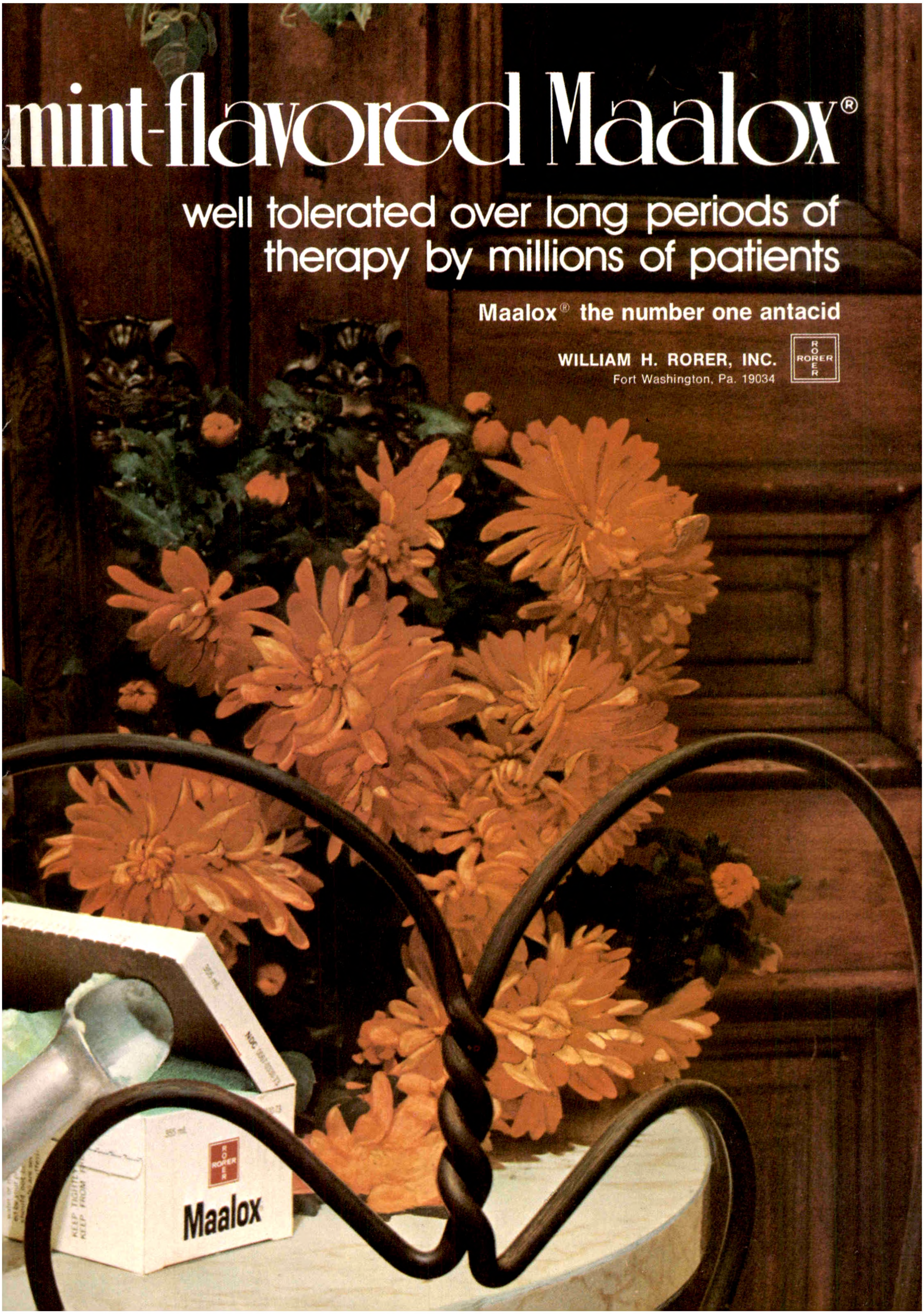
Keflex®
cephalexin monohydrate
continues a trend–
third price reduction in three years*
250-mg.† Pulvules®–
reduced 32%*

400894

Lilly

Additional information available to the profession on request.
Eli Lilly and Company • Indianapolis, Indiana 46206

cool, soothing



mint-flavored Maalox®

well tolerated over long periods of
therapy by millions of patients

Maalox® the number one antacid

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034

RORER

Similar...yet

Two analgesics effective for the relief of mild to moderate pain

Darvon® Compound-65

65 mg. propoxyphene hydrochloride, 227 mg. aspirin,
162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

Darvon® Compound-65
propoxyphene hydrochloride, aspirin,
phenacetin, and caffeine

Actions: Propoxyphene hydrochloride is a mild analgesic structurally related to the narcotic analgesic methadone; though propoxyphene's general pharmacologic properties are those of the narcotics as a group, it does not compare with them in analgesic potency.

The combination of propoxyphene with a mixture of aspirin, phenacetin, and caffeine (APC compound) produces greater analgesia than that produced by either propoxyphene or APC compound administered alone.

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

Administration and Dosage: A narcotic prescription is not required.

Darvon Compound-65 is given orally. The usual dosage is 1 Pulvule® every four hours as needed for pain. Each Pulvule contains 65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine.

How Supplied: Pulvules Darvon® Compound-65 (propoxyphene hydrochloride, aspirin, phenacetin, and caffeine, Lilly), in bottles of 500, in Identi-Dose® (unit dose medication, Lilly) in boxes of 100, and in Rx Paks (prescription packages, Lilly) in bottles of 100, in 25 packages of 30, and in 20 packages of 50.

[050374]

different

new

Darvocet-N® 100

100 mg. propoxyphene napsylate and 650 mg. acetaminophen

contains no aspirin

Darvocet-N®
and
Darvocet-N® 100
propoxyphene napsylate with acetaminophen

Description: Each tablet of Darvocet-N contains 50 mg. propoxyphene napsylate and 325 mg. acetaminophen.
Each tablet of Darvocet-N 100 contains 100 mg. propoxyphene napsylate and 650 mg. acetaminophen.

Indication: These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychosis and convulsions.

Administration and Dosage: A narcotic prescription is not required.

These products are given orally. The usual dose is 100 mg. propoxyphene napsylate and 650 mg. acetaminophen every four hours as needed for pain.

Drug Interactions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

How Supplied: Tablets Darvocet-N® and Darvocet-N® 100 (propoxyphene napsylate with acetaminophen, Lilly), in an Rx Pak (prescription package, Lilly) in 20 packages of 50, in bottles of 100 (Rx Pak) and 500, and in Identi-Dose® (unit dose medication, Lilly) in boxes of 100. Darvocet-N 100 is also available in an Rx Pak in 25 packages of 30. [102373]

Additional information available to the profession on request.

Lilly

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Eli Lilly and Company
Indianapolis, Indiana 46206

An effective non
for post-op EMETIC

Unsurpassed efficacy

Control of emesis has been shown to be equivalent to that achieved with Compazine® (prochlorperazine) and other potent phenothiazines in well-controlled clinical studies.*

Well tolerated

The parenteral solution is non-irritating and does not produce pain at the site of injection. Drowsiness appears to be the most common adverse reaction. Other more significant reactions have been reported. Please refer to the package insert.

phenothiazine
CONtrol

Characteristically nonhypotensive

Emete-con™ (benzquinamide HCl) may be used in marginally hypotensive patients since it does not characteristically cause or potentiate hypotension.

No respiratory depression

Emete-con does not characteristically cause respiratory depression or potentiate CNS depressants.

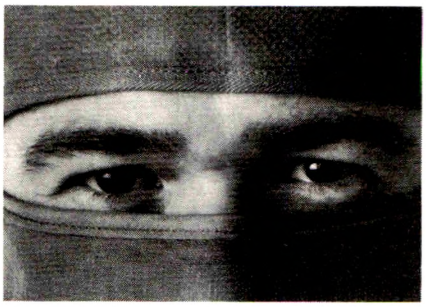
Usual adult dose: IM-50 mg., IV-25 mg.

Emete-con™
(benzquinamide HCl) IM/IV
post-op EMETIC-CONtrol

*Please see next page for a bibliography of clinical studies.

For prescribing information, including adverse reactions and contraindications, please see following page.

Emete-con™
(benzquinamide HCl)$^{IM}/_{IV}$
post-op EMETIC-CONtrol



PRESCRIBING INFORMATION
Emete-con™ (benzquinamide hydrochloride)
For Intramuscular and Intravenous Use

Description. Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide hydrochloride) is N, N-diethyl-1,3,4,6,7, 11b-hexahydro-2-hydroxy-9, 10-dimethoxy-2H-benzo [a] quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5$. HCl and the molecular weight is 441.

Emete-con for injection contains benzquinamide hydrochloride equivalent to 50 mg/vial of benzquinamide and 0.45 mg/vial of citric acid. When reconstituted with 2.2 ml of proper diluent, each vial yields 2 ml of a solution containing benzquinamide hydrochloride equivalent to 25 mg/ml of benzquinamide and 0.02% citric acid. When reconstituted this product maintains its potency for 14 days at room temperature.

Actions. Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con (benzquinamide hydrochloride) should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected—*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg—1.0 mg/kg))

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con (benzquinamide hydrochloride) should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Intravenous: 25 mg (0.2 mg/kg—0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended.

This preparation must be initially reconstituted with 2.2 ml of Sterile Water for Injection, Bacteriostatic Water for Injection with benzyl alcohol or with methylparaben and propylparaben. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml. which maintains its potency for 14 days at room temperature.

Overdosage. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

Caution. Federal law prohibits dispensing without prescription.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

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Emete-con™
(benzquinamide HCl)$^{IM}/_{IV}$
post-op EMETIC-CONtrol

Each vial contains benzquinamide hydrochloride equivalent to 50 mg. of benzquinamide with 0.45 mg. of citric acid.

Ergot Intoxication:

Historical Review and Description of Unusual Clinical Manifestations

G. CRAIG MERHOFF, M.D., JOHN M. PORTER, M.D.

From the Vascular Surgical Service, Department of Surgery, University of Oregon Medical School, Portland, Oregon 97201

Clinical ergotism as seen today results almost exclusively from the excessive intake of ergotamine tartrate in the treatment of migraine headache. Although both gangrenous and convulsive symptoms are seen in naturally occurring ergotism resulting from the ingestion of fungus infected rye, only gangrenous ergotism has been reported following the excessive ingestion of ergotamine tartrate. The symptoms of both iatrogenic and naturally occurring ergotism appear to result from regional ischemia caused by ergot induced vasospasm. This report discribes experiences in the diagnosis and management of two patients with unusual manifestations of iatrogenic ergotism. One patient presented with ischemia of all extremities and bilateral foot drop probably due to ischemic damage to the common peroneal nerves, a finding not previously described in ergot intoxication. The foot drop totally resolved in several months following the discontinuation of ergot. A second patient presented with unilateral leg ischemia and transient monocular blindness, both of which resolved after discontinuation of ergot. Both patients displayed typical angiographic findings of ergotism. There is no convincing evidence that any treatment other than discontinuation of ergotamine is of benefit in the treatment of iatrogenic ergotism.

ERGOTISM, which once occurred in great epidemics, has virtually disappeared since recognition of the etiology of the naturally occurring disease. Epidemic ergotism has been largely replaced by ergotism resulting from the medicinal use of the ergot alkaloids. Iatrogenic ergotism, although occurring infrequently, often presents a diagnostic problem. For a physician to encounter a case of classic ergotism is sufficiently unusual to make the diagnosis difficult, and for him to encounter a patient with an unusual manifestation of ergotism, possibly without a clear history of drug usage, makes early diagnosis virtually impossible. We have recently treated two patients with unusual manifestaitons of ergotism, and in neither of these patients was the diagnosis made early in the course of the disease. Our experience with these two patients prompted us to review the history of ergotism as well as the pharmacology and toxicity of the various ergot preparations. This review, together with a description of the clinical course of the two patients, forms the basis of this report.

Historical Review

The first Western reference to ergotism was in the ninth century A.D. and described an epidemic of gangrenous ergotism wherein "a great plague of swollen blisters consumed the people by a loathsome rot so that their limbs were loosened and fell off before death."[4] Convulsive ergotism was first described in the eleventh century as a "fire which twisted the people."[4] A mixed epidemic with both gangrenous and convulsive manifestations was described later in the eleventh century. Large epidemics of ergotism occurred in Europe, Scandinavia, Bohemia, and Russia from the ninth through the nineteenth century, at which time the frequency declined sharply, although epidemics occurred into this century including a small epidemic in France in 1951.[2,4,23,39,43]

Epidemics of ergotism usually presented purely gangrenous or purely convulsive manifestations, although several mixed epidemics were reported from Russia.[4] A

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satisfactory explanation for this repeated observation has never been presented, although hypovitaminosis A has been circumstantially implicated as an etiologic factor in convulsive ergotism.[4,18,50] The latter appears with lower doses of ergot than does the gangrenous form, which may explain death from convulsive ergotism without the appearance of gangrene, but does not explain death from gangrenous ergotism without the appearance of convulsions. Also, inadequately explained is why gangrenous ergotism occurred most frequently in France and only rarely in Germany, where the convulsive form predominated.[4] Possible pharmacologic differences between the ergots of different areas is unproven. A number of factors have been felt to predispose to the development of epidemic ergotism in individual patients, including hypovitaminosis A and C, hepatic disease, malnutrition, reanal disease, sepsis, vascular disease and thyrotoxicosis.[4,8,14,45,50]

In 1676, it was recognized that epidemic ergotism resulted from eating foods, usually breads or cereals, made from rye which was contaminated with the fungus, *Claviceps purpurea*.[4] The sclerotium of this fungus is ergot, and the fungus elaborates the ergot alkaloids as well as several other pharmacologically active compounds, including histamine and tyramine. That ergot epidemics persisted beyond that time appears due in large part to the resistance to change of an uneducated public, and, strikingly, to the defense of ergot by a number of Europe's most learned men.[4]

The earliest Western description of the medicinal use of ergot was in 1582 when it was reported useful as a uterine stimulant.[4] In 1820, ergot was added to the U.S. Pharmacopoeia for obsetetrical use, although the potential toxic effects of the drug were clearly recognized at that time.[4,25,36] The earliest reference to the use of ergot for the treatment of migraine headache was in 1883.[17]

Ergotamine was isolated by Stoll in 1918 and its salt, ergotamine tartrate, proven to be a potent and stable compound which could be chemically assayed.[4,44] Reports of iatrogenic ergotism, almost exclusively attributable to ergotamine, have appeared since that time, including those by Oginz 1930,[41] Gould *et al.* 1936,[26] Yater and Cahill 1936,[50] vonStorch 1938,[45] Thompson *et al.* 1950,[48] Young and Humphries 1961,[51] Hudgson and Hart 1964,[32] and most recently, McLoughlen and Sanders 1972.[38]

Pharmacologic Effects

Naturally occurring ergot contains several pharmacologically active substances other than the ergot alkaloids; however, their role in the production of epidemic ergotism and in the toxicity of whole ergot preparations is unknown. Chemically and pharmacologically the ergot alkaloids are divided into three categories: amino acid alkaloids (ergotamine); dihydrogenated amino acid alkaloids (dihydroergotamine and dihydroergotoxine), and the amine alkaloids (ergonovine).[25,44]

The major pharmacologic effects of the ergot alkaloids include smooth muscle stimulation, central sympatholytic activity, and peripheral alpha adrenergic blockade. Smooth muscle stimulation is most evident as vasoconstriction and as uterine contraction. Vasoconstriction appears to result from stimulation of the alpha receptors to which the drug is tightly bound, while uterine contraction results from direct smooth muscle stimulation exclusive of the alpha receptors.[33] While all of the ergot preparations, except the amine alkaloids, are bound to the alpha receptors, the ability of the various preparations to produce alpha receptor stimulation varies widely.

The central sympatholytic property results from drug action directly on the medullary vasomotor centers and occurs with lower drug dosages than are required for peripheral alpha receptor blockade.[20,21] Other effects upon the central nervous system include the stimulation of emesis and the inhibition of prolactin secretion.[6,19,22,25]

The amino acid alkaloids (e.g., ergotamine) are the most potent vasoconstrictors, displaying no oxytocic effects when given orally. This class of drugs has been most widely used in the treatment of migraine headache. The amine alkaloids (e.g., ergonovine and methylergonovine) are potent oxytocics with relatively weak vasoconstricting actions and no sympatholytic or alpha blocking properties.[25] A summary of the pharmacologic actions of the various ergot preparations is presented in Table 1.

TABLE 1. *Pharmacologic Properties of Ergot Derivatives*

Class	Action			
	Vasconstriction	Oxytocic	α-Blocker	Sympatholytic
Amino Acid Alkaloids (Ergotamine Tartrate)	Most Active	Highly Active but of Delayed Onset, Not Active Orally	Active	Active
Dihydrogenated Amino Acid Alkaloids				
(Dihydroergotamine)	Active but less than Above	Active on Pregnant Human Uterus	Most Active	Most Active
(Dihydroergotoxine)	None			
Amine Alkaloids (Ergonovine and Methylergonovine)	Slight	Most Active	None	?

Toxicity

The most important toxic effect of the ergot alkaloids is vasospasm which can effect virtually any vessel, including the coronary arteries and the splanchnic circulation.[3,5,16,24,33,35,45] Prolonged vasospasm is expressed clinically as ergotism of either the gangrenous or convulsive types, or rarely as both. Symptoms common to both forms of ergotism include lassitude, emesis, lumbar muscle pain, ischemic cutaneous vesicles on the hands or feet, diarrhea, and impaired mental function.[4] The following descriptions of the two forms of ergotism are derived from observations made during the great epidemics when the victims had ingested a mixture of ergots plus other substances of unknown significance. There have been far fewer observations of patients with ergotism resulting from the ingestion of a pharmacologically pure substance, but these observations would generally agree with the classic descriptions. The notable exception is that convulsive ergotism has not been reported following the use of pure ergot compounds, although Oginz noted a report in the German literature of a patient who developed acute pseudotabes dorsalis while receiving fluid extract of ergot containing ergotamine tartrate and unknown other substances.[40,41] This resolved when the ergot was withdrawn.

Gangrenous ergotism is characterized by pulseless ischemic limbs which may be covered with blisters. If ergot ingestion continues, the patient develops dry gangrene which may lead to autoamputation or, less commonly, suppurative gangrene and sepsis. This is frequently preceded by weeks of intense burning pain known as St. Anthony's fire, although in cases of massive intoxication as little as 24 hours may elapse between ergot ingestion and the onset of gangrene. Although the lower extremities are most often affected, the upper extremities may be involved as well, and occasionally may be the only extremities affected.[7,10,12,17,32] The ischemic process is usually symmetric, although unilateral limb involvement has been reported.

Symptomatic vasospasm, although most common in the extremities, may affect any organ system. Severe splanchnic vasospasm may occur, occasionally with the production of intestinal infarction.[4,5] Renal artery vasoconstriction may be sufficiently severe to present as acute renal failure.[16] Coronary artery vasoconstriction may become manifest as angina pectoris, or, rarely, as acute myocardial infarction.[24,42,45] Ophthalmic artery vasospasm has been described occasionally with the clinical symptoms of transient or permanent blindness.[4,36]

Convulsive ergotism in its most severe form is characterized by repeated grand mal seizures leading to death. Milder forms are characterized by formication, an apparently invariable symptom in this condition. Increasing intoxication leads to clonic contractions of digits, or entire extremities, accompanied by severe pain. Chronic weakness, contractures, pain, hemiparesis, paraplegia, pseudotabes dorsalis and sensory disturbances including anesthesia of the extremities may occur and are frequently permanent. Mental disturbances ranging from transient disorientation to permanent dementia have been described. A number of ophthalmic complications have been reported following convulsive ergotism, including mydriasis, amblyopia, cataracts, retinal damage, optic nerve damage and glaucoma.[13,15,36]

Although gangrenous and convulsive ergotism share certain symptoms, the two are usually clinically distinct. Gangrenous erogtism is rarely accompanied by convulsions and convulsive ergotism is rarely accompanied by gangrene, although in both types, a common pathologic abnormality is severe vasospasm. If this persists, proliferation of the endothelium and thrombosis may occur. This may be accompanied by hyaline degeneration and fibrosis of the vascular wall, apparently resulting from loss of vascular wall nutrition from luminal blood flow as well as from spasm of the vasa vasora.[26,35,48,50] Direct neurotoxicity has not been described and the neurologic manifestations are thought to be secondary to ischemia.[3,4,30,35,45,50] Hemorrhagic infarction of the brain and degeneration of the posterior and lateral columns of the spinal cord have occurred rarely.[50]

Case Reports

Case I. A 61-year old Caucasian female presented to our emergency room with a three-week history of severe pain in both lower extremities. The patient was a known alcoholic with documented mild chronic liver disease. Her legs were noted to be cool and moderately cyanotic with delayed capillary filling and diminished sensation of both feet. No pulses could be palpated in either lower extremity below the femoral artery. The patient's hands were cool and moderately cyanotic and no pulses could be palpated distal to the brachial artery in either arm. The patient had been examined six weeks earlier in the Outpatient Clinic at which time she was noted to have normal pulses to palpation in all extremities and a normal neurologic examination. The patient denied the use of drugs. She was admitted to the hospital with a diagnosis of possible vasculitis. Twenty-four hours later angiography was performed revealing diffuse, severe vascular spasm (Fig. 1A). Upon repeat specific questioning, the patient reluctantly admitted using two Cafergot^{R}* suppositories daily for the preceding three weeks for headache.

Two days following admission her peripheral pulses were all normal to palpation; however, at this time she manifested bilateral foot drop as well as diminished pain, temperature, vibration, and position sensation in both legs. A bone marrow examination revealed no megaloblastic changes. Lower extremity nerve conduction and electromyographic determinations were performed and showed no conduction in the deep peroneal nerves and fibrillation potentials in the extensor brevis muscles bilaterally. The patient was maintained on bed rest and within two weeks had totally

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* Cafergot^{R} (Sandoz). Each suppository contains ergotamine tartrate 2.0 mg and caffeine 100 mg.

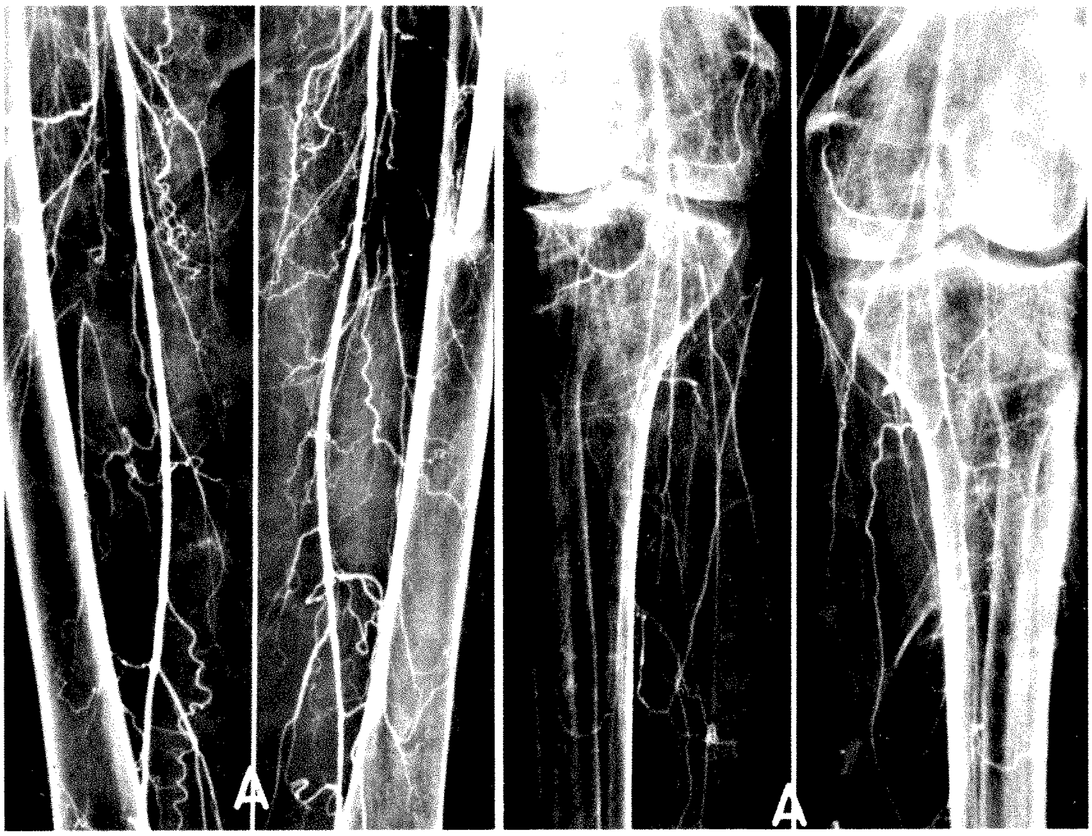

Fig. 1A. Arteriogram of first patient 24 hours after hospital admission. Moderate narrowing of the superficial femoral artery is present, with marked spasm of the popliteal artery and almost total obliteration of the branches of the popliteal trifurcation.

healed the superficial foot ulcers and showed some improvement in the bilateral foot drop. A repeat arteriogram was normal (Fig. 1B). Repeat nerve conduction determinations and electromyography at monthly intervals demonstrated progressive reinervation. At three months, the foot drop had totally resolved and the patient had normal sensation over the feet, although she complained of severe dysesthesias in both lower extremities.

Case II. A 34-year-old Caucasian male was referred to our institution for evaluation of suspected peripheral vascular disease. The patient had a five-year history of temporal headaches, thought to be histamine cephalgia, for which he had been taking two or three Cafergot^R suppositories daily for several months. Prior to this he had taken 8–10 suppositories weekly for two years. He presented to his local physician with a three-week history of left leg pain which had progressed to severe claudication on minimal exertion. Physical examination revealed no pulses palpable distal to the left femoral artery. Femoral arteriography was performed and showed severe vasospasm of the left femoral artery with no evidence of atherosclerotic obstruction. Ergotism was not suspected, and the patient continued to take the ergot suppositories. Despite continued use of ergot, the left leg improved partially; however, one day prior to admission to our institution, he noted the sudden onset of blurred vision in his left eye, followed by a total loss of vision in the eye. He underwent a complete ophthalmologic examination on the same day and was noted to have severe retinal vasospasm and retinal pallor. A central scotoma was documented and the visual acuity was found to vary between 20/200 and 20/400. When the patient arrived at our hospital the next day, he was still complaining of left leg pain as well as blurred vision in his left eye, although he felt both were improving slightly.

On examination all pulses were palpable although quite weak in both arms and in the right leg. Only a weak femoral artery pulse could be palpated in the left leg with no pulses palpable distally. The use of the Cafergot^R suppositories was discontinued, and 24 hours later a repeat complete ophthalmologic examination was normal. Within 48 hours all pulses were normal to palpation, including the previously absent left popliteal, posterior tibial, and dorsalis pedis pulses. The patient's severe headaches continued daily requiring narcotics for relief. Over the next several weeks, the headaches decreased dramatically in severity, requiring only occasional codeine tablets. His left leg symptoms resolved completely. On his most recent examination, six months following discharge, he was totally asymptomatic except for mild occasional headaches requiring the use of one to three codeine tablets per week.

Discussion

Both patients were taking massive overdoses of ergotamine tartrate, as can be seen from Table 2 which lists the manufacturer's maximal recommended dosage for the various routes of administration. The first patient had used 28 mgm of ergotamine tartrate by rectum weekly for three weeks without having previously used the drug. She developed acute toxicity after three weeks of usage, although this was not initially appreciated because of her denial of drug usage. The second patient had used 28–42 mgm of ergotamine tartrate by rectum weekly for several months, and prior to that time, he had used 20 mgm or more per week for several years. He had never developed any toxic symptoms until about three weeks before admission to our hospital. These examples

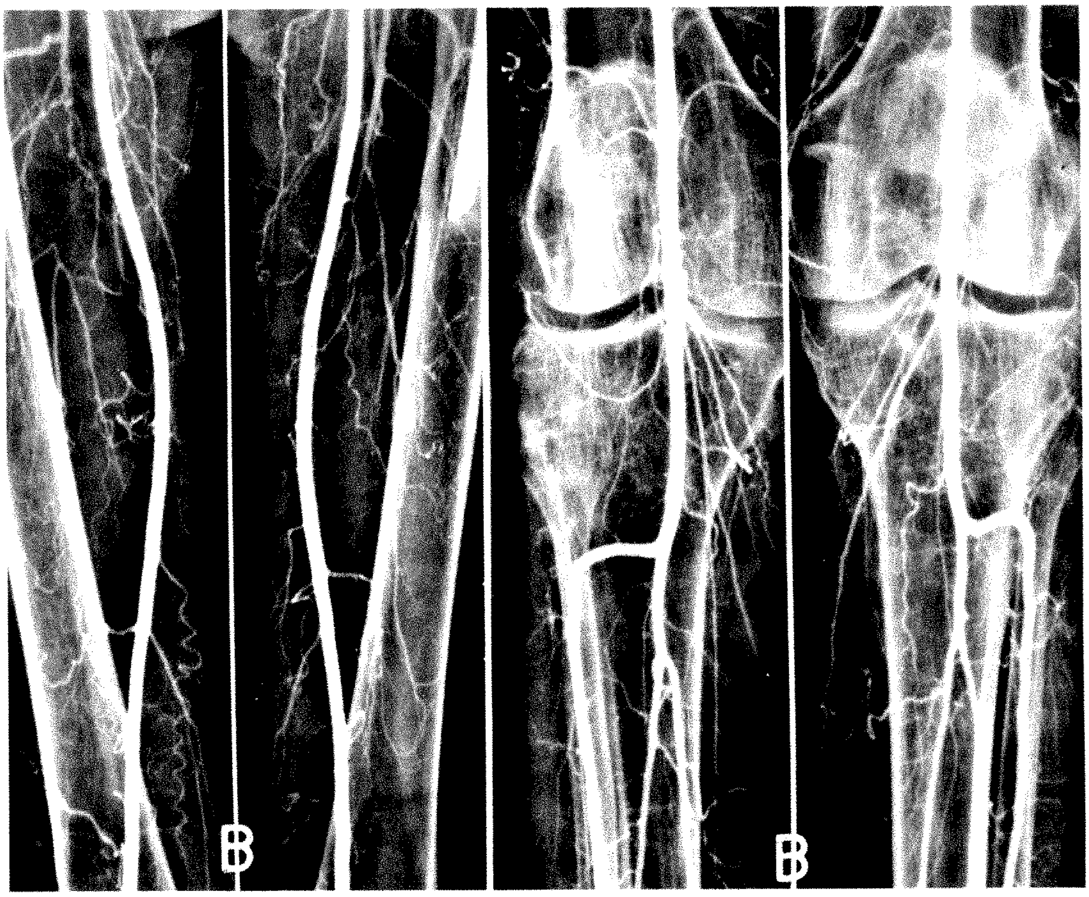

FIG. 1B. Normal arteriogram two weeks later on same patient as in Fig. 1A.

clearly illustrate the tremendous variability in ergot tolerance among patients. It has long been recognized that some patients are quite sensitive to ergots, while others tolerate doses considered to be in the toxic range for years without developing symptoms. An unresolved question is why a patient who has tolerated large doses of ergot for a prolonged period of time should suddenly develop symptoms of intoxication. The actual incidence of ergot intoxication has been estimated at less than 0.01% of patients taking ergot preparations, although side effects such as nausea, vomiting, abdominal and leg pain occur in about 10% of patients taking ergots orally or rectally.

The initial presentation of the first patient with symmetric ischemia worse in the lower extremities is typical of gangrenous ergotism, although she rapidly developed peripheral neurological symptoms. The development of bilateral foot drop with no evidence of nerve conduction followed by return to normal in three months is strong evidence of peripheral ischemic neuropathy. Although peripheral nerve damage has been described in epidemic ergotism, there has been no previous report of reversible foot drop following natural or iatrogenic ergotism.

The second patient's presentation with unilateral lower extremity ischemia is unusual, but has been previously reported, as has the spontaneous improvement of limb ischemia despite the continued use of ergots.[17,42] The visual symptoms and findings are rarely seen, but appear similar to those described by Kravitz in 1935 and by Gupta more recently.[27,36] However, the lesion spared the optic nerve in our patient and involved the nerve in the two previous reports. This patient also demonstrated the phenomenon of rebound headache which has been frequently described following the withdrawal of ergots. Most patients treat this rebound headache with additional ergot, to which they usually respond, and in so doing perpetuate an unrelenting cycle which may end in ergotism. Complete ergot withdrawal usually produces severe headaches for about five days at which point they usually subside.[19,42]

Both patients were diagnosed following angiography, a situaiton which has been reported by others.[16,30,34,38,45,47] The angiographic findings of ergotism as first de-

TABLE 2. *Dosage for Ergotamine Tartrate**

Route	Single Dose	Maximum Per Attack	Maximum Per Week
Oral	1 mg	6 mg	11 mg
Rectal	2 mg	4 mg	8 mg
Parenteral	0.25–0.5 mg		1.0 mg

* Sandoz.

scribed by Yater and Cahill in 1936 when they reported "the main arteries of the leg to be smooth in outline and apparently normal down to the lower third of the leg when they faded out into a point" were present in both patients.[50] These authors also noted collaterals around the vasospastic segment. These collateral vessels have been observed by others and have been noted to disappear following dilatation of the major vessel upon withdrawal of ergots.[12,13,28,34] Recent reports of the angiographic findings of ergotism have confirmed the original description.[1,13,16,24,28,37,47,49,51]

The treatment of both these patients was entirely expectant, and they both improved within a few days as the drug was metabolized. Others have reported similar results.[13,14,25,26,31,43,47] Numerous pharmacologic agents have been used in an effort to achieve vasodilatation. These include ethyl alcohol, amyl nitrite, scopolamine, theophyllin, tolazoline, hydergine, phentolamine, sodium nicotinate, papaverine, procaine, and lidocaine.[1,7–12,16,26,29,30,32,38,48] None of these has been of any immediate clinical benefit except for sodium nicotinate and tolazoline, and the benefits from these drugs have been confined to single case reports.[46,48,51] Direct sympathetic blockade using conduction anesthetic techniques has occasionally appeared to be of some benefit, as has the performance of regional sympathectomy.[32,37,38]

It is difficult to understand how vasodilatation could result from the use of vasodilating drugs or sympathectomy since ergotamine is tightly bound to the alpha receptors. Attempts to experimentally displace ergotamine from the alpha receptors with phenoxybenzamine have been unsuccessful.[33] In addition, it has long been recognized that ergotamine is a pure vasoconstrictor in the sympathectomized limb.[6] Anticoagulation with heparin or the use of dextran may be of benefit, since thrombosis may occur in the spastic vascular segments.

We feel that the initial treatment of ergot intoxication should be the simple discontinuation of the ergot preparation. If there appears to be impending tissue loss, it would appear reasonable to use heparinization and/or dextran and intra-arterial tolazoline or intravenous sodium nicotinate. If there is no response to these measures, regional sympathetic blockade may be attempted, although as noted, there is no firm evidence that this is beneficial.

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Effect of Allopurinol on the Preservation of Ischemic Kidneys Perfused with Plasma or Plasma Substitutes

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Canine kidneys were autotransplanted into nephrectomized dogs after exposure to room temperature for 40–90 minutes and preservation for 24 hours by hypothermic bloodless pulsatile perfusiin. Three perfusates were used; cryoprecipitated pooled dogs' plasma, human albumin, and human plasmanate. Perfusion after periods of warm ischemia resulted in irreversible renal damage, unless allopurinol was added to the perfusate and fed to the dogs. Thus, metabolic manipulation is capable of protecting tissues in the face of severe ischemic insult, even when using plasma substitutes for perfusion.

KIDNEY PRESERVATION for periods of 24–48 hours is now routine clinical practice,[2] the most important limiting factor being the period of warm ischemia prior to preservation.[3] We have previously demonstrated that the treatment of canine kidneys with allopurinol during perfusion with cryoprecipitated plasma significantly minimized the damage induced by a one-hour period of warm ischemia.[10] Furthermore, if the animal was given allopurinol after transplantation, in addition to the perfusion treatment, there were no deaths related to severe renal ischemia.[10]

A second problem remains in preservation; the development of plasma substitutes to eliminate the time-consuming and costly method of plasma cryoprecipitation. Plasma substitutes can be used, but not if a prolonged period of warm ischemia precedes preservation.[7] The present study was designed to assess the effect of allopurinol in protecting against ischemic damage when added to a perfusate of plasma or plasma substitutes.

Materials and Methods

Thirty-six adult mongrel dogs weighing 15–24 kg were anesthetized with sodium methohexital for induction and with halothane for maintenance. Through a left lateral subcostal incision, the left kidney was removed and placed at 25 C for a period of time ranging from 40 to 90 minutes. It was then flushed with cold (4 C) Ringer's lactate solution containing heparin (10,000 U/L) and procaine (1 gm/L) until the venous effluent was clear. Subsequently, each kidney was preserved for 24 hours by pulsatile perfusion at 7 C, pH 7.4, pO_2 200 mm Hg, pulse rate 60 and systolic perfusion pressure of 60 mmHg.[9] The perfusion system was primed with 700 ml of the perfusate to be used. Flow rate, perfusion pressure, kidney weight and perfusate electrolytes and lactic acid dehydrogenase (LDH) were determined every six hours. After preservation and autotransplantation, immediate contralateral nephrectomy was performed.

Six groups of kidneys were included with six kidneys in each group. Groups I and II were exposed to 90 minutes of warm ischemia and perfused with cryoprecipitated plasma prepared by Belzer's technique.[1] Groups III and IV were exposed to 60 minutes warm ischemia and were perfused with human albumin 25% (Cutter Laboratories). Groups V and VI were exposed to 40 minutes warm ischemia and perfused commercial human plasmanate (Cutter Laboratories). Methylprednisolone (500 mg/L) was added to all perfusates. Allopurinol (500 mg/L) was added to the perfusate of kidneys in Groups II, IV and VI. The animals in Groups II, IV and VI were fed allopurinol (100 mg/kg/day) for four days prior to and 10 days after transplantation.

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TABLE 1. *24 Hour Perfusion Characteristics of the Control and the Kidneys Treated with Allopurinol* (Mean Values ± SD)

			Flow Rate (ml/min/gm)		K+§ (mEq/L)		LDH‖ (U/100ml)		Weight Gain (% from Control)
Groups	Perfusates	Allopurinol Treatment	Initial Value	Final Value	Initial Value	Final Value	Initial Value	Final Value	Final Value
I	CPP*	–	0.7 ± 0.2	0.6 ± 0.3	4.5 ± 0.7	6.2 ± 1.0	82 ± 35.1	175 ± 17.5	8.5 ± 1.5
II	CPP*	+	0.7 ± 0.2	1.2 ± 0.2	5.3 ± 0.6	5.9 ± 1.4	65 ± 28.4	200 ± 19.5	7.2 ± 2.0
III	A†	–	0.9 ± 0.2	0.8 ± 0.3	5.5 ± 1.2	6.4 ± 1.2	75 ± 15.7	185 ± 25.5	10.5 ± 1.2
IV	A†	+	1.0 ± 0.2	1.4 ± 0.3	4.2 ± 1.3	5.7 ± 1.2	56 ± 25.7	275 ± 12.5	8.5 ± 2.3
V	p‡	–	0.4 ± 0.1	0.5 ± 0.2	4.5 ± 0.7	6.2 ± 0.9	85 ± 30.5	135 ± 15.8	11.5 ± 3.0
VI	p‡	+	0.5 ± 0.2	0.9 ± 0.3	4.3 ± 0.7	6.7 ± 1.1	74 ± 21.3	145 ± 18.5	9.8 ± 2.5

* Cryoprecipiated plasma (90 min. ischemia).
† Human Albumin (60 min. ischemia).
‡ Human plasmanate (40 min. ischemia).
§ Normal values 3.8–5.2 mEq/L.
‖ Normal values 40–80 U/100 ml.

All animals were examined daily until death. Renal function was determined by daily serum creatinine (normal 0.6 to 1.6 mg%) and uric acid (normal 3.2 to 7.5 mg%) levels. The experiment was terminated 30 days following transplantation. Postmortem examination with kidney biopsy was performed in all cases.

Results

The perfusion characteristics of the kidney in each group are shown in Table 1. All kidneys demonstrated poor initial post-ischemic perfusate flow which remained the same or even deteriorated in kidneys not perfused with allopurinol. When allopurinol was added to the perfusates, a significant improvement in perfusate flow was noticed by 24 hours of perfusion. The other perfusion parameters (weight gain, potassium and LHD), however, did not improve with the addition of allopurinol (Table 1). In addition, there were some differences in perfusion characteristics depending on the type of perfusate used; for example, the kidneys with the lowest flow and greatest weight gain were perfused with plasmanate. All kidneys demonstrated high perfusate potassium and LDH levels by the end of the 24 hours perfusion.

Table 2 summarizes the state of renal function and survival of dogs autotransplanted with preserved kidneys after periods of warm ischemia. Dogs autotransplanted with kidneys perfused with albumin or plasmanate were almost all dead of uremia by 30 days. Eighty-four per cent of cohort dogs survived if allopurinol had been added to the perfusate. Similarly, only one of six kidneys perfused with cryoprecipitated plasma after 90 minutes warm ischemia was capable of supporting life. All kidneys perfused with cryoprecipitated plasma plus allopurinol functioned normally by two weeks after transplantation.

Discussion

It is well known that hypoxic tissues lose purine intermediate compounds to the surrounding fluids, but recover and reconvert them if oxygen is restored,[4,6] since the cell possesses resynthesis pathways such that hypoxanthine and higher compounds can be reconverted to ATP.[12] Once degradation of the nucleotides has proceeded beyond the xanthine level, however, they become irreversibly lost to the nucleotide pool.[5,11] Allopurinol, a xanthine oxidase inhibitor, appears to act by inhibition of the further degradation of xanthine. DeWall and associates[5]

TABLE 2. *Survival and Renal Function of Kidneys Autotransplanted After Warm Ischemia and 24 Hypothermic Pulsatile Perfusion*

Group	Perfusates	Ischemia Time (min)	Allopurinol Treatment	Serum Creatinine at one week§	Serum Uric Acid at one week§	Days to return to Normal Serum Creatinine‖	Survival**
I	CPP*	90	–	8.2 ± 1.5	5.6 ± 1.0	No return	16% (1/6)
II	CPP*	90	+	2.1 ± 0.9	4.3 ± 0.7	9.5 ± 1.8	100% (6/6)
III	A†	60	–	12.1 ± 2.5	4.8 ± 1.6	No return	0% (0/6)
IV	A†	60	+	2.9 ± 0.8	3.9 ± 0.3	13.1 ± 8.7	84% (5/6)
V	P‡	40	–	11.8 ± 1.7	5.6 ± 1.0	No return in 5. 15 days in one.	0% (0/6)
VI	P‡	40	+	1.8 ± 0.5	4.1 ± 0.7	9.5 ± 1.8	84% (5/6)

* Cryoprecipitated plasma
† Human Albumin
‡ Human Plasmanate
§ mg% (Mean values ± SD)
‖ Mean values ± SD
** More than 30 days with normal creatinine

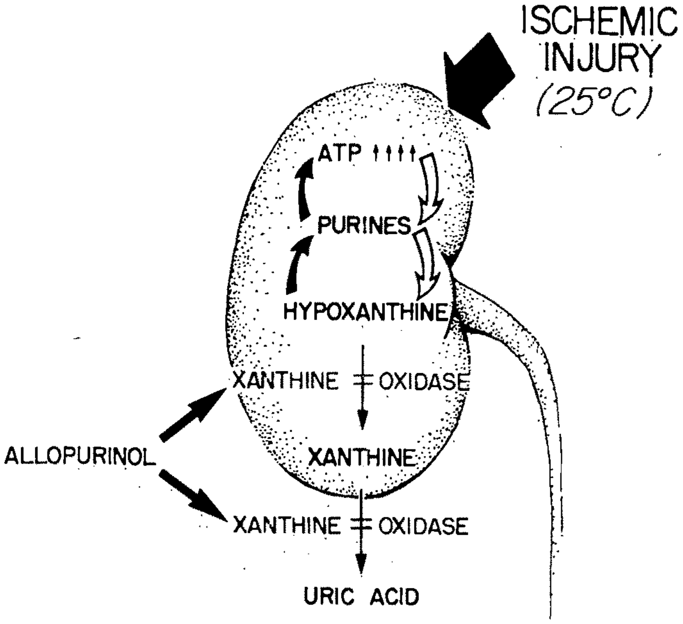

FIG. 1. General metabolic pathway of the purines when degradation has been inhibited by allopurinol during hypoxia. Allopurinol appears to prevent ATP loss in the ischemic kidney.

have studied the response of the ischemic myocardium to allopurinol. They stated that the recovery of the damaged muscle is based on the utilization of the pool of functional purine bases which would be available for reformation of high energy nucleotides. A similar sequence probably takes place in the ischemically damaged kidney. The treatment of the kidneys with allopurinol probably allows the purine intermediates to be reconverted to ATP, if sufficient oxygen becomes available after the initial ischemic injury (Fig. 1).

Warm ischemic damage of the preserved kidneys is an important cause of injury, the severity of which increases with the duration of ischemia. The absence of oxygen precludes the utilization of the citric acid cycle and increases anaerobic metabolism with accumulation of lactic acid and other anaerobic by-products. The maintenance of celluar volume is an active energy consuming process which is dependent on the sodium pump.[8] Lack of energy causes pump failure which leads to accumulation of sodium and water in the cells and cellular swelling. Continuous hypothermic perfusion with various oxygenated perfusates permits only minimal cellular swelling and partially reverses the anoxic injury by allowing aerobic metabolism to recommence. Although certain perfusates are better than others, a kidney subjected to room temperature for more than 60 minutes without oxygen fails to sustain life if the kidney is then perfused for 24 hours with either cryoprecipitated plasma or albumin. Even periods of ischemia as short as 40 minutes seriously damage kidneys perfused with plasmanate.

This study confirms the protective effect of allopurinol in the prolongation of tissue and organ survival time in the face of hypoxia even when less than optimal perfusates are utilized. The potential immediate clinical application to transplantation is obvious.

In addition, allopurinol may well prove to be a useful additive in the search for simple, less expensive and readily available substrates for cryoprecipitated plasma as a perfusate for organ preservation.

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Erythrocyte 2, 3-Diphosphoglycerate in Endotoxic Shock in the Subhuman Primate:

Response to Fluid and/or Methylprednisolone Succinate

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The effects of shock as a result of *Escherichia coli* endotoxin on certain hemodynamic and biochemical parameters and mortality were studied in the baboon. The ability of methylprednisolone succinate (MPS) in massive doses and/or rapid infusion of a buffered electrolyte solution to influence the results was then examined. Shock secondary to *Escherichia coli* endotoxin was associated with a decrease in RBC 2,3-DPG. This fall in RBC 2,3-DPG was not significantly influenced by MPS. Likewise, MPS did not prevent the changes in oxygen metabolism or systemic hemodynamics, nor was it associated with any decrease in mortality associated with endotoxic shock. Buffered electrolyte solution therapy improved both hemodynamics and mortality, but did not significantly protect against changes in RBC 2,3-DPG.

A DECREASE in erythrocyte 2,3-diphosphoglycerate (RBC 2,3-DPG) in the patient with septic shock was reported by Sugerman *et al.*,[11] whereas Naylor *et al.*[7] found no change in RBC 2,3-DPG in the rhesus monkey after four hours of endotoxic shock. A decrease in 2,3-DPG, other factors excluded, would shift the oxyhemoglobin dissociation curve to the left with an increased affinity of hemoglobin for oxygen and thus might lead to a decrease in tissue oxygenation. McConn and associates[5] have demonstrated that RBC 2,3-DPG can be increased *in vitro* by incubation with methylprednisolone succinate. This study was performed to determine the response of RBC 2,3-DPG to endotoxic shock in the baboon and to determine if this response and the mortality could be altered with methylprednisolone succinate or buffered electrolyte solution.

Method

Preparation of Animals

Twenty-four healthy baboons (*Papio doguera*) weighing 13–27 kg were sedated with Sernylan (phenylcyclidine hydrochloride) 1 mgm/kg, given intramuscularly and secured in an upright position in a primate restraining chair. A catheter (polyvinyl chloride 200) was placed in each femoral artery and vein. One of the venous catheters was flow-directed into the right atrium for measuring central venous pressure. The remaining catheters were used to monitor arterial pressure, obtain arterial samples and inject drugs via a venous line. Animals were given 30 minutes to recover from Sernylan prior to the experiment. No additional anesthesia was administered.

Arterial pressure was continually monitored on a heat stylus recorder through a strain-gauge manometer. Central venous pressure was determined at each sampling period with a water manometer zeroed at the estimated level of the right atrium. Cardiac output was determined at each sampling time by the dye dilution method using indocyanine green and a Beckman cardiodensitometer. This instrument was calibrated initially for each experiment using the animal's own blood and a known concentration of dye. No correction was made for change of hematocrit during the course of the experiment. In our previous experience, the small changes noted have had no significant effect on the calculation of cardiac output. Arterial and central venous pO_2, pCO_2 and pH were determined on a blood gas analyzer calibrated prior to each experiment with known gas mixtures. Red blood cell 2,3-DPG was determined using a modification of the microfluorometric method of Keitt.[3] Arterial lactate was measured using the modification of the enzyme analysis method described by Bergmeyer.[1]

Experimental Procedure

E. coli endotoxin (Difco 055b5)* was mixed in saline to a concentration of 1 mgm/ml and infused into the

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TABLE 1. *Animals in Group*

(Death)			
Group		Treatment	Results
Control	Shock	No Rx*	6 (6)†
17	17	BFL	3 (1)
		MPS	3 (3)
		BFL + MPS	5 (1)
Control	Sham	Sham	6 (0)
6	6		

* See text for explanation of treatments.
† Numbers in parentheses represent animals that died.

femoral vein at the rate of 5 mgm/minute until the arterial pressure fell below 60 mm Hg (beginning of shock period).

Samples were obtained and measurements were made: a) three times, ten minutes apart during the control period, b) at the beginning of the shock period, and c) every hour thereafter for seven hours or until death.

One of four types of therapy was randomly chosen and begun immediately after the samples were taken at the beginning of the shock period. The treatment modalities were: a) No therapy (No Rx), b) Intravenous buffered electrolyte solution* (BFL) given at 5 ml/kg/min. for 20 minutes, c) Methylprednisolone succinate† (MPS) given intravenously, 30 mgm/kg body weight, or d) BFL plus MPS.

Sham studies were conducted on six baboons by sedating the animals, inserting the catheters, and obtaining all measurements and samples for seven hours without giving endotoxin.

For analysis of the data, sampling times compared were control, shock, and the last sample before death. The difference between control and shock and between control and the last sample for each experimental group was evaluated by a paired t test. The differences between control and the last sample for each group were then compared to each other by analysis of variance using an "f" statistic.

TABLE 2. *Erythrocyte 2, 3-DPG*
(mM/Liter erythrocytes)

		Treatment	Last Sample
Control	Shock	No Rx	−1.2 ± 0.7*
4.7 ± 1.0	−0.3 ± 1.1*	BFL	−0.4 ± 0.3
		MPS	−0.6 ± 1.0
		BFL + MPS	+0.1 ± 0.9
Control	Sham	Sham	−0.5 ± 0.7
4.4 ± 0.7	+1.0 ± 4.1		

Erythrocyte 2, 3-DPG decreased 0.3 mM/L erythrocytes with endotoxic shock and with "No Rx" dropped 1.2 mM/L erythrocytes, when compared to control. The "last sample" is change from "control."
*Significant change.

TABLE 3. *Arterial PO₂*
(mm Hg)

		Treatment	Last Sample
Control	Shock	No Rx	+ 4.6 ± 25.1
77.8 ± 8.5	+3.5 ± 8.9	BFL	+26.5 ± 16.7
		MPS	− 0.7 ± 19.7
		BFL + MPS	+ 7.3 ± 19.0
Control	Sham	Sham	− 0.5 ± 7.4
76.2 ± 4.8	+1.0 ± 6.3		

"Last sample" is change from "control."

Results

Of the 24 animals given endotoxin, 20 developed shock (blood pressure less than 60 mm Hg). The amount of endotoxin required varied from 20 to 208 mgm (average 168 mgm or 8.4 mgm/kg). In four animals the blood pressure never dropped below 100 mm Hg in spite of 400, 625, 650, and 800 mgm of endotoxin respectively. No other parameter in these animals changed during the study period. One of these animals was found dead the next morning; autopsy did not suggest the cause.

Of the remaining 20 animals, three died shortly after the onset of shock and are not included in this study.

Of the 17 animals included in this report, the mean period of shock before the last sample was: a) 270 minutes in the "No Rx" group; b) 400 minutes in the "BFL" group; c) 260 minutes in the "MPS" group; and d) 300 minutes in the "BFL + MPS" group.

The survival-mortality data (Table 1) for the animals in each group demonstrated universal death in the "No Rx" and "MPS" groups and complete survival in the "sham" group.

Erythrocyte 2,3-DPG (Table 2) decreased with the development of shock and fell further when no treatment was given. Although the change with no treatment was significant from control, it was not different from changes in 2,3-DPG noted in the other groups using an "f" statistic analysis..

Arterial pO_2 (Table 3) showed no significant change.

Venous pO_2 (Table 4) fell in the last samples of the "No Rx" group and of the "MPS" group. Both of these changes from control were statistically significant from the changes from control in the other groups ($p < 0.05$) when evaluated by an "f" statistic.

Cardiac output (Table 5) decreased at the beginning of shock and remained decreased in the "No Rx" group

TABLE 4. *Venous PO₂*
(mm Hg)

		Treatment	Last Sample
Control	Shock	No Rx	−11.8 ± 6.1*
34.6 ± 4.1	+0.9 ± 9.4	BFL	+ 1.5 ± 6.8
		MPS	−15.0 ± 12.0*
		BFL + MPS	+ 0.9 ± 0.2
Control	Sham	Sham	− 1.5 ± 4.3
36.8 ± 3.4	−0.2 ± 4.5		

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* Normosol,ᴿ Abbott.
† Kindly supplied as Solumedrolᴿ by The Upjohn Company, Kalamazoo, Michigan.

TABLE 5. *Cardiac Output*
(Liters Per Minute)

		Treatment	Last Sample
Control	Shock	No Rx	−0.70 ± 0.30*
1.25 ± 0.31	−0.33 ± 0.30*	BFL	−0.25 ± 0.07
		MPS	−0.57 ± 0.40*
		BFL + MPS	−0.30 ± 0.20
Control	Sham	Sham	−0.03 ± 0.30
1.15 ± 0.36	−0.12 ± 0.20		

and "MPS" group. These changes from control were significantly different from the changes noted in the other groups.

Arterial pH (Table 6) fell in the "No Rx" and "MPS" groups. These changes from control were not significantly different from other changes from control ($p > 0.05$).

Arterial lactate (Table 7) increased in all but the "sham" group. These changes from control were all significantly different from the changes noted in the "sham" animals.

Arterial pCO_2 (Table 8) was variable and no significant changes were noted.

Arterial blood pressure (Table 9) decreased in the shock period as dictated by the experimental model. It remained significantly depressed in the "No Rx" and in the "MPS" groups. The depressed blood pressure in the "BFL" and "BFL + MPS" groups was due to the one animal in each group that died just after the last sample. These latter changes were not significantly different from control.

Discussion

There was a 26% decrease in RBC 2,3-DPG noted in these studies of the baboon in endotoxic shock for four hours. Miller *et al.*[6] have reported that a change in RBC 2,3-DPG of 0.420 mmole/l of packed RBC changes the hemoglobin dissociation curve 1 mm at the p50 point. Thus the mean decrease in RBC 2,3-DPG of 1.2 mmoles/l RBC in these experiments would shift the dissociation curve 2.9 mm at the p50 point. If this is true, the isolated effect of 2,3-DPG in this series of experiments might be expected to cause a mean 11% decrease in oxygen delivery. Whether other factors (pCO_2, pH) block the 2,3-DPG mediated shift, and the effects on the availability of oxygen for tissue was not examined in this study. In a separate series of investigations, Proctor *et al.*[10] were unable to document changes in tissue oxygen consumption in association with alteration in RBC 2,3-DPG content.

TABLE 6. *Arterial Ph*

		Treatment	Last Sample
Control	Shock	No Rx	−0.30 ± 0.25*
7.46 ± 0.03	−0.02 ± 0.06	BFL	−0.03 ± 0.18
		MPS	−0.26 ± 0.42
		BFL + MPS	−0.02 ± 0.21
Control	Sham	Sham	−0.02 ± 0.04
7.47 ± 0.05	−0.03 ± 0.05		

TABLE 7. *Arterial Lactate*
(mM/L)

		Treatment	Last Sample
Control	Shock	No Rx	+8.5 ± 5.0*
1.8 ± 0.9	+1.0 ± 1.6*	BFL	+6.9 ± 2.8*
		MPS	+6.6 ± 4.3*
		BFL + MPS	+4.5 ± 2.2*
Control	Sham	Sham	+0.1 ± 1.0
2.0 ± 1.5	−0.5 ± 0.6		

Some of the current reports of cardiorespiratory alterations found in septic shock are outlined in Table 10. The variations in the findings are attributed to differences in experimental design. The decrease in venous pO_2, oxygen consumption, and a-v oxygen difference suggests that a decrease in the ability of hemoglobin to desaturate and a decreased cardiac output are responsible for the decreased oxygen consumption. The inability to improve biochemical, hemodynamic, or survival data by preventing a fall in 2,3-DPG in our experiments suggests that RBC 2,3-DPG does not play a major role in the abnormalities produced by endotoxin. Proctor[10] has suggested that the fall in cardiac output is the main abnormality leading to inadequate tissue oxygenation in low flow states, such as hemorrhagic and endotoxic shock and decreases in 2,3-DPG play a definable but relatively minor role in further decreasing tissue oxygenation.

TABLE 8. *Arterial PCO_2*
(mm Hg)

		Treatment	Last Sample
Control	Shock	No Rx	− 4.2 ± 12.0
33.3 ± 5.3	−3.9 ± 10.0	BFL	−15.4 ± 8.0
		MPS	+ 0.7 ± 18.8
		BFL + MPS	− 6.2 ± 13.0*
Control	Sham	Sham	− 6.2 ± 3.5*
35.1 ± 5.7	−1.8 ± 3.6		

In the experiments currently reported, it would appear that rapid and massive buffered electrolyte therapy afforded some protection from death. This altered the decrease in cardiac output, decrease in central venous pO_2, metabolic acidosis, and fall in blood pressure that developed in the groups not receiving buffered electrolyte

TABLE 9. *Mean Arterial Pressure*
(mm Hg)

		Treatment	Last Sample
Control	Shock	No Rx	−48 ± 38*
109 ± 22	−54 ± 23*	BFL	−31 ± 30
		MPS	−54 ± 15*
		BFL + MPS	−42 ± 46
Control	Sham	Sham	+ 5 ± 12
109 ± 27	+ 7 ± 15		

TABLE 10. *Cardiorespiratory Alterations in Septic Shock*

Author	Subject	Agent	Length of shock	2, 3-DPG	p50	PaO_2 (p) or O_2 sat (s)	PvO_2 (p) or O_2 sat (s)	$PaCO_2$	ApH	$A\text{-}VO_2$	O_2 consump.	Cardiac Output
Guenter, 1969[2]	Rhesus monkey	Endotoxin Live *E. coli*	2.5-4 hrs.			decr. then incr. (p) N. C.		decr. decr.	decr. decr.	decr.	decr.	decr. decr. incr.
Miller, 1970[6]	Humans	Sepsis	variable	decr.	decr.							
Sugerman, 1970[11]	Humans	Sepsis	variable	decr.			decr. (p)			decr.	decr.	variable
Pool, 1971[8]	Monkey	Live *E. Coli*	up to 7 hrs.			decr.	decr.	decr.	decr.	incr.		
Priano, 1971[9]	Dogs	Live *E. coli*				sl decr. (p)		decr.	N. C.	incr.	decr.	incr.
Lundsgaard-Hansen, 1972[4]	Rabbit	Endotoxin	up to 8 hrs.			N. C. (s)			decr.	N. C.		
Naylor, 1972[7]	Rhesus monkey	Endotoxin		N. C.	N. C.	N. C. (p)	N. C. (p)	decr.	decr.		N. C.	decr.
Wilson, 1972[12]	Humans	Sepsis	variable								decr.	
Present Series	Baboon	Endotoxin	2 to 5 hrs.	decr.		N. C. (p)	decr. (p)	N. C.				decr.

N. C. = no change

therapy. It did not prevent the rise in arterial lactate.

The fall in RBC 2,3-DPG was not significantly influenced by methylprednisolone succinate given in massive doses, nor did MPS by itself alter the fall in cardiac output, the decrease in blood pressure, the decrease in pH, or the decrease in central venous pO_2. There was no improvement in mortality, biochemical or hemodynamic changes in the groups receiving the methylprednisolone succinate compared to those that did not.

The answers to the specific question posed in this study of a baboon model with endotoxic shock are: a) RBC 2,3-DPG decreases with endotoxic shock in the subhuman primate studied. b) Based on the development of metabolic acidosis and an increase in serum lactate, an inadequate supply of oxygen reached the tissues. Although the decreased RBC 2,3-DPG could lead to decrease in the delivery of oxygen to the tissues, changes in 2,3-DPG were not sufficient to explain the apparent profound deficiency in tissue oxygenation. Thus, the alterations that developed in oxygen metabolism in septic shock are related to a variety of factors including the marked decrease in cardiac output and are not entirely due to abnormalities in the transport of oxygen by hemoglobin. c) Massive, rapid infusion of a buffered electrolyte solution afforded the best protection against changes in biochemical and hemodynamic parameters and mortality. Although the change in RBC 2,3-DPG was less in the animals that received methylprednisolone succinate and/or buffered electrolyte solution, this was not satistically significant in the limited number of experiments.

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Propranolol in the Surgical Management of Thyrotoxicosis

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Forty-nine thyrotoxic patients prepared for partial thyroidectomy with the β-adrenoceptor blocking drug, propranolol, and iodine are compared with 42 patients prepared with carbimazole and iodine. The age and sex distribution of the two groups were comparable, but patients with obstructive airways disease and possible cardiac insufficiency were excluded from preparation with propranolol. The mean duration of preoperative treatment with propranolol was 40 days, compared with 89 days for carbimazole. Propranolol treated patients had lower pulse rates before and after operation. The serum $PB^{127}I$ values immediately before and after operation were higher in the propranolol group than in the carbimazole group, but were the same in both groups one and four months after operation. The incidence of hypothyroidism at one year after operation was 30% in the carbimazole prepared patients and 31% in the propranolol patients. Serum calcium levels were higher in the propranolol group at the time of operation. No adverse effects from the use of propranolol and at operation the thyroid gland prepared with propranolol was firmer, less friable, more easily mobilised and less likely to bleed than the gland prepared with carbimazole. There is, consequently, less risk of damage to the parathyroid glands and recurrent laryngeal nerves. However, the basal metabolic rate remains high on propranolol therapy and very careful supervision is advised.

INITIAL ATTEMPTS at producing sympathetic blockade in the management of thyrotoxicosis were surgical[2,5] but recently various pharmacological agents, including reserpine,[1] guanethidine[12] and alpha-methyldopa,[11] have been introduced in an attempt to reduce the excessive adrenergic activity which contributes to the clinical features of this condition. Following the introduction of propranolol, beta-adrenoceptor blockade has been shown to modify many of the features of thyrotoxicosis, and though the place of beta-blockade in the management of this condition has not yet been clearly defined, propranolol is used successfully in the treatment of thyroid crisis[9] and as an adjuvant to radio-iodine therapy.[8]

Patients with thyrotoxicosis are usually prepared for surgery with conventional thiourea derivates but recently Lee *et al.*[6] have described their experience with propranolol in this situation. The mechanisms of action of these drugs are dissimilar and it is unlikely that either influences the natural history of the disease.[7] In this paper we compare the use of these drugs in the preparation of thyrotoxic patients for surgery and try to determine whether patients prepared with propranolol differ in any respect before, during or after operation from those prepared with carbimazole.

Patients and Methods

In a study commencing in July 1970, 132 patients underwent thyroidectomy for thyrotoxicosis. Our usual method of preoperative preparation was to make the patient euthyroid with carbimazole and then give iodine for up to ten days before operation. In our early experience with propranolol, this drug was prescribed in addition to carbimazole before operation, but with increasing knowledge of the effects of β-blockade in this situation, it eventually became possible to omit carbimazole

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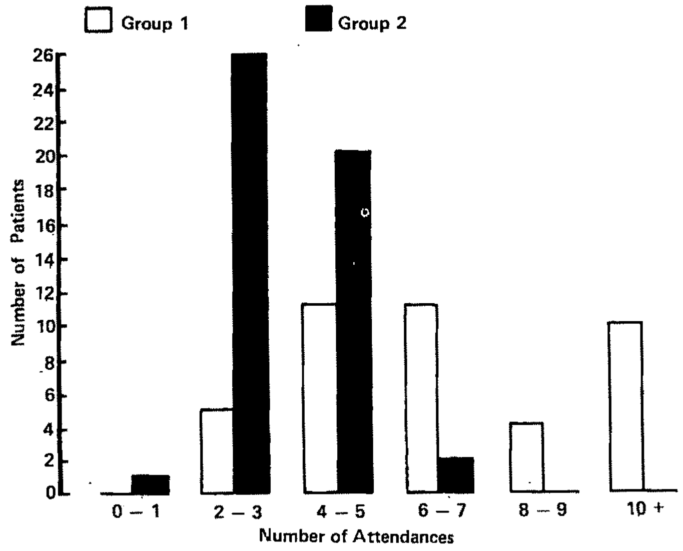

FIG. 1. The number of out-patient visits by patients prepared for thyroidectomy with carbimazole (Group 1) and with propranolol (Group 2).

therapy. Apart from excluding patients with possible cardiac or obstructive airways disease from propranolol treatment, no attempt was made to select patients for any particular preoperative regime. Forty-one patients had combined therapy with carbimazole and propranolol and are not discussed further. Forty-two patients (seven men) were prepared with carbimazole (Group 1) and 49 patients (seven men) with propranolol (Group 2). The age range of the patients prepared with carbimazole was 15–60 years. Six patients were 20 years old or less and three were 50 years or older. In the propranolol group, the age range was 15–64 years. Six patients were aged 20 years or less and five were 50 years or more. All were given iodine preoperatively for periods varying between three and ten days. Patients in Group 1 received varying doses of carbimazole and in each case the dose was the minimum necessary to make the patient clinically and biochemically euthyroid. The initial dose was 40 mg or 60 mg daily given in four divided doses. The maintenance dose before operation varied from 2.5 mg twice daily to 5 mg thrice daily. The total daily dose of propranolol, except for two patients, was 120 mg daily given as 40 mg eight-hourly. The two remaining patients were prescribed 40 mg six-hourly, and we have continued to use this latter dose for subsequent patients.

TABLE 1. *Mean Pulse Rates in Thyrotoxic Patients Undergoing Partial Thyroidectomy*
(Means ± S.E.M.)

	Beginning of Operation	End of Operation	24 Hours	48 Hours
Group 1 (Carbimazole)	81 ± 2	80 ± 2	89 ± 2	90 ± 2
Group 2 (Propranolol)	70 ± 1	73 ± 1	81 ± 1	80 ± 1

TABLE 2. *Average Blood Pressures in Thyrotoxic Patients Undergoing Partial Thyroidectomy*
(Means ± S.E.M.)

		Beginning of Operation	End of Operation
Group 1 (Carbimazole)	Systolic	130 ± 3	126 ± 3
	Diastolic	78 ± 2	78 ± 1
Group 2 (Propranolol)	Systolic	128 ± 3	118 ± 3
	Diastolic	76 ± 2	78 ± 2

Preoperative medication was with omnopon and either scopolamine or atropine, and atropine was also given intraoperatively if the anaesthetist considered that the pulse rate was falling unduly. Approximately 15 minutes before operation 8–12 ml of lignocaine (0.5%) containing adrenaline (1:200,000) were infiltrated into the wound area to reduce bleeding. Anaesthesia was maintained with halothane, nitrous oxide and oxygen. The pulse rate was measured four-hourly from 24 hours before operation until the time of discharge and hourly for 24 hours after operation. Blood pressure was recorded on admission, at the beginning, during and at the end of operation, and thereafter until the pressure had stabilised. A record was kept of total gland mass, which was calculated from the measured weight of resected thyroid tissue and remnant weight estimated during operation.[4]

Serum levels of protein bound iodine ($PB^{127}I$), calcium, alkaline phosphatase and proteins were estimated at the patient's first appearance, during drug therapy, immediately before and after operation, at 24 and 48 hours, and at one month and four months after operation.

Where propranolol was used in preoperative preparation, the patients early in the series were retained for an extra day, but later we reverted to our customary practice of discharge on the second or third day after operation. Propranolol therapy was maintained until the seventh postoperative day.

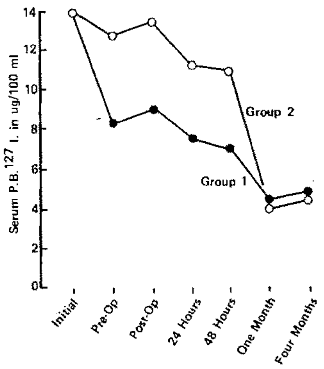

FIG. 2. The serum $PB^{127}I$ values in patients prepared for thyroidectomy with carbimazole (Group 1) and with propranolol (Group 2).

Results

The mean duration of treatment was 40 days for patients prepared with propranolol compared with 89 with carbimazole. The number of outpatient attendances from initial visit to the time of operation is given in Fig. 1.

At the beginning of operation, the mean pulse rate in Group 2 was significantly lower than in Group 1 ($p < 0.001$). The propranolol treated patients had also significantly lower pulse rates at 24 hours ($p < 0.005$) and 48 hours ($p < 0.001$) after operation (Table 1). Average systolic and diastolic blood pressures at the beginning and end of operation were similar in both groups, although the systolic pressure at the end of operation was lower in Group 2 ($p < 0.05$) than in Group 1 (Table 2).

The mean serum PB^{127}I values were the same at the time of initial examination (Fig. 2) but were significantly higher ($p < 0.001$) in the propranolol prepared patients immediately pre- and postoperatively and at 24 and 48 hours after operation. At one month and four months after operation, there were no significant differences.

Serum calcium levels corrected for serum protein concentration were similar when the patients were first seen (Fig. 3), but were higher in the propranolol treated patients preoperatively, postoperatively and at 24 hours after operation ($p < 0.001$), and at 48 hours after operation ($p < 0.005$). These differences were not evident at one and four months after operation. In general there appeared to be a parallel reduction in the serum alkaline phosphatase levels in the two groups (Fig. 4) with the exception of the estimation at one month after operation which was higher in patients prepared with propranolol ($p < 0.05$).

Using the criteria we employ for assessing postoperative thyroid status,[8] the incidence of hypothyroidism following operation was 30% in the carbimazole prepared patients and 31% in the propranolol group.

Mean total gland mass was 51.0 g for the carbimazole prepared patients and 50.3 g for the propranolol group.

Discussion

Many of the features of hyperthyroidism are mediated through the autonomic nervous system and the beneficial effects of propranolol are the result of β-adrenoceptor blockade and suppression of those symptoms and signs related to increased sympathetic activity. Propranolol does not interfere with thyroidal iodine uptake, and thyroid hormone synthesis and release are unchanged. This contrasts with the action of carbimazole, which inhibits, at least, the iodide oxidation and organification steps of thyroxine synthesis, leading to reduced production of thyroid hormones.

Our use of propranolol in the preparation of the thyrotoxic patient for surgery has been cautious, and initially we employed it in conjunction with carbimazole. Recognizing the risks of precipitating heart failure and bronchospasm, we were careful to exclude patients with a history of cardiac insufficiency or obstructive airways disease and none of the patients had any significant associated disease. In the event we did not find it necessary to stop propranolol or reduce its dosage because of side effects.

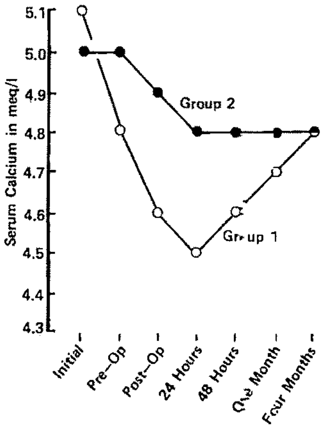

FIG. 3. The serum calcium levels in patients prepared for thyroidectomy with carbimazole (Group 1) and with propranolol (Group 2).

The difference in blood pressure between the two groups was small, but the pulse rate in the propranolol prepared patients was significantly lower both before and after operation. Reduction of pulse rate is of subjective benefit to the thyrotoxic patient, though the absence of reflex tachycardia is a potential hazard if the patient is exposed to shock from any cause. On seven occasions the anaesthetist gave intraoperative atropine as a prophylactic measure, but in no patient has bradycardia or hypotension been a problem.

We have confirmed that patients treated with propranolol were biochemically thyrotoxic at the time of operation. Serum PB^{127}I levels were still elevated at 48 hours after operation, and for this reason propranolol therapy was maintained for the first postoperative week. It is perhaps too early to compare the effect of the two forms of preoperative management on the incidence of postoperative hypothyroidism, but the results at four months after operation indicate that there is no difference between the groups in this respect.

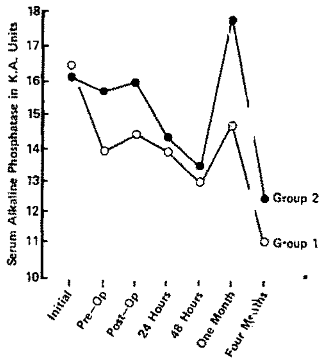

FIG. 4. The serum alkaline phosphatase levels in patients prepared for thyroidectomy with carbimazole (Group 1) and with propranolol (Group 2).

The values for serum calcium and serum alkaline phosphatase are consistent with the bone disease which occurs in thyrotoxicosis, and which is presumed to relate high circulating levels of thyroid hormone. Except for the initial estimation when the patient was first seen, serum calcium values were higher in Group 2 than in Group 1 until 48 hours after operation. We would postulate that whereas thyrotoxic osteodystrophy may heal if the patient is made biochemically euthyroid with carbimazole, it is less likely that healing will occur with propranolol in the dose we have employed. Fears have been expressed that prolonged propranolol therapy might induce a progressive osteodystrophy,[7] and that short term therapy might precipitate dangerous hypocalcaemia.[10] Of the former we have no experience; of the latter we have no evidence.

If a new form of treatment is to merit consideration, it must offer significant advantages over previous methods of treatment. Propranolol administration does not interfere with biochemical or isotopic tests of thyroid activity, and therapy need not be delayed until diagnostic tests are completed. In contrast with carbimazole therapy, where symptomatic relief may not be achieved for several days or weeks, subjective improvement or propranolol may occur within a matter of hours. In this study, the average duration of preoperative therapy with propranolol was 40 days, which was less than half for the carbimazole patients. Latterly preoperative preparation has been reduced in several patients to approximately 14 days, and two patients were operated upon after preparation for five and three days respectively. The number of clinic attendances can be greatly reduced, and when a satisfactory response to propranolol has been confirmed—and this is not unusual at the patient's second visit to the clinic—it is possible to predict and arrange the date of operation.

Technical surgical advantages are difficult to quantify. Though total gland mass was the same in both groups, the thyroid gland prepared with propranolol is of firmer consistence, is less friable and has a reduced risk of tearing when compared with the gland prepared with carbimazole. These differences have been mentioned recently by Lee *et al.*[6] Mobilisation of the gland and resection of the lobes are easier and haemorrhage is less. In consequence there is less risk of interference with the parathyroid glands and recurrent laryngeal nerves. These benefits, added to easier and more rapid control of symptoms, suggest that preparation for partial thyroidectomy with propranolol should be considered in the management of the thyrotoxic patient. However, it should be remembered that propranolol does not affect all the features of hyperthyroidism and in particular has little effect on the basal metabolic rate. Until more information is available we would suggest that this use of propranolol should be carefully supervised.

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The Effects of Distention and Obstruction on the Accumulation of Fluid in the Lumen of Small Bowel of Dogs

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Fluid accumulation in either the obstructed upper or lower intestinal segments of the dog was found in most animals to be negligible. Distention pressures of 25 cm of water tended to reduce fluid accumulation within the intestinal lumen. These studies suggest that if the dog is comparable to man, the intraluminal accumulation of fluid in the obstructed small bowel of man might be due to alterations in blood supply to the intestine, rather than to obstruction per se, or the accumulated fluid originates proximal to the jejunum.

ALTHOUGH there has been considerable progress in understanding the pathophysiological changes during small bowel obstruction, the death rate from prolonged ileus remains high. Dehydration, hypovolemia and electrolyte imbalance are considered by surgeons today to be significant complications which occur in patients with nonstrangulating obstruction of small intestine. Since the studies of Hartwell and Houget in 1912[8] nearly 60 years ago, the value of parenteral water and electrolyte administration in patients with intestinal obstruction has been known and widely accepted. The prolongation of lives in dogs with high intestinal obstruction by infusing these moities subcutaneously, stimulated research into losses of fluid and electrolytes in obstruction and led to the classic studies of Gamble and his associates in 1951[6] who showed that the depletion of water and salts were predominantly responsible for the so-called "toxic factor" in intestinal obstruction.

Although previous investigators have demonstrated that plasma proteins escape from the vascular compartment during intestinal obstruction, it is not known exactly into which compartment the plasma proteins are lost. Enquist and associates[4,11] observed a drop in plasma, blood and interstitial volume in dogs during intestinal obstruction. Moore in 1959[10] stated that 5–9 L of fluid may be sequestered in the distended gut in obstructive ileus. It is logical to assume that loss of plasma proteins may follow the sequestration of fluid.

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Normally only a minute fraction of albumin is lost into the gastrointestinal tract.[7,20] Wetterfors[19] postulated that the gastrointestinal tract might be a source of increased albumin loss during injury. Plasma albumin levels are quite constant in health but alterations are known to occur following major trauma or operation. Howard and associates[5] found that trauma to visceral organs results in a characteristic decrease in the serum albumin concentration with little change in the globulin fraction. Albumin is a relatively small protein moiety with a molecular weight of 68,000 as opposed to the gamma globulins with molecular weights up to 1,000,000. Consequently the preferential loss of a smaller molecular weight protein during injury would suggest that the loss of plasma proteins occurs as a result of leakage from the circulation rather than from its metabolism.

The current investigation was undertaken to determine whether the gastrointestinal tract could be a site of loss of plasma proteins during intestinal obstruction. A study was made of the amounts of fluid accumulating within intestinal segments at various times after ligation. Numerous previous investigations have suggested that there should be marked fluid accumulation within obstructed intestinal segments.[3,10,13] There have been practically no studies, however, in which the net accumulation of fluid has been actually measured in intestinal segments following ligation and obstruction. Since dogs

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were used in most of the previous studies involving intestinal absorption, dogs were also selected for use in this series of experiments.

Materials and Methods

The effects of distention on the proximal and distal intestine were studied in a series of 42 dogs of either sex, weighing 24–45 kg. Four groups of experiments were performed. The experimental conditions under which each group was studied are described below.

The effects of short-term distention were studied in the *first* group of 8 dogs. Prior to study, the dogs were fasted overnight, but they were allowed to have water. An initial intravenous dose of 30 mg/kg body weight of pentothal sodium was used for anesthesia. Supplementary doses were given to maintain a suitable plane of anesthesia. The femoral artery was exposed and catheterized in order to measure blood pressure. The abdominal cavity was opened through a midline incision with a minimum amount of bleeding. A ligature of umbilical tape was placed around the jejunum 10 cm below the ligament of Treitz. A stab wound was made in the upper ileum 60 cm below the ligature in the jejunum. A rubber catheter was introduced through the stab wound and directed proximally toward the upper ligature for a distance of about 40 cm. The 40 cm portion of the catheter inside the intestine had multiple perforations to facilitate aspiration of the intestinal contents. Umbilical tape was used to tie the catheter in place and at the same time obstruct the ileum, resulting in a 60 cm closed, obstructed segment. At the beginning of the experiment, the intestinal segment was aspirated and its contents measured and retained for analysis. The catheter was then closed for a control period of 1 hour. After the 1 hour control period the contents of the intestinal segment were again aspirated and retained for analysis. At that time the catheter was connected to a Sanborn transducer which was in turn connected to the Sanborn 760 series recording system. Air was then introduced into the catheter to distend the intestine. A distention pressure of 20–25 cm water pressure was subsequently maintained in the intestinal segment. After the first hour of distention the intestinal fluid was withdrawn, measured and an aliquot was taken for analysis. The aspirated fluid was returned to the intestinal loop and allowed to remain there for another hour. Air was again introduced through the catheter in order to distend the intestine at a pressure of 20–25 cm H_2O pressure. After the second hour of distention, the intestinal contents were removed and retained for analysis. Throughout the course of the experiment the intra-abdominal temperature was monitored with a Yellow Springs Instrument Co., telethermometer. The intra-abdominal temperature was maintained at 37–39 C by means of a heat lamp. The blood pressure was also monitored and remained at 110–124 mm Hg. At the end of the experiment, the distended loop was excised and weighed. The volume of the intestinal fluid was measured and recorded and its sodium and potassium content was determined.

The effects of long-term distention and obstruction of the *proximal* small intestine were studied in a *second* group of 24 dogs. Using aseptic technique the abdominal cavity was opened. A 60 cm segment of upper small intestine was tied off in a manner similar to that which was done in the *first* group of dogs. In half of the dogs the intestinal segment was inflated with 50–60 cc of air by means of a syringe and needle. The intestinal catheter used in the *first* group of dogs was omitted. Unnecessary handling of the abdominal viscera was avoided. The abdominal cavity was closed, and the dogs were given intraperitoneally, 1 million units of penicillin and 1.25 g of dihydrostreptomycin. The dogs were also given 1000 ml of saline intravenously during and immediately following the operative procedure. Food was retained, but the dogs were allowed to drink water freely. These dogs were divided into 4 subgroups. These subgroups, consisting of 8, 10, 4 and 2 dogs, were studied at 24, 48, 72 and 96 hours respectively after ligation of their intestine. At that time the abdominal cavity was opened and the obstructed segment was excised and weighed. The accumulated intraluminal fluid was measured and analyzed for sodium and potassium and in some instances for total proteins and albumin.

The effects of obstruction and distention of the *distal* small intestine were studied in the *third* group of 4 dogs. In this series of experiments, a 60 cm segment of small intestine immediately proximal to the ileocecal valve was obstructed at both ends, using umbilical tape as ligatures. The intestinal segment was injected with air in a manner similar to that used in the previous series of animals. The dogs were allowed to have water, but food was retained. The dogs were sacrificed after 72 hours. Measurements of volume, sodium, potassium and total protein were made as described previously.

The effects of distention and obstruction on the absorption of fluid injected into the intestinal lumen was studied in a *fourth* group of 6 dogs. The dogs were fasted for 24 hours prior to their use. The small bowel was ligated at 20 cm intervals to make 12 closed loops. The distal most tie was applied just above the ileo-cecal valve. Alternate loops were filled with 20–25 ml of saline containing blue dextran (25 mg/ml having a molecular weight of 2 million). One million units of penicillin and 1.25 g of dihydrostreptomycin were given intraperitoneally in 5 ml solution and the abdomen was closed. After 24 hours the abdominal cavity was reopened and each of the intestinal segments were again filled with 20–25 ml of saline.

TABLE 1. *Effect of Distention on the Fulid Accumulation in the Proximal Small Intestine (Group I)*

	Fluid Collected Immediately After Isolation of Intestinal Segment*			Control 1 Hr. Without Distention*			1 Hr. After Distention†‡			2 Hr. After Distention§‡		
No. Dog	ml	Na/mEq/L	K/mEq/L	ml	Na/mEq/L	K/mEq/L	ml	Na/mEq/L	K/mEq/L	ml	Na/mEq/L	K/mEq/L
1	25	150	8	3	120	6.8	147	165	6.4	87	162	6.8
2	0	—	—	0	—	—	0	—	—	0	—	—
3	5	160	7.5	4	144	6.9	20	145	6.3	54	152	5.9
4	14	152	4	4	152	6.4	5	165	8.7	0	—	—
5	8	160	8.3	4	148	8.2	0	—	—	0	—	—
6	0	—	—	0	—	—	0	—	—	0	—	—
7	0	—	—	0	—	—	0	—	—	0	—	—
8	0	—	—	0	—	—	0	—	—	0	—	—
Mean	6.5	155	6.9	1.8	141.0	7.0	21.5	158.3	7.1	17.6	157.0	6.4
±S.D.	9.0	5.2	1.9	2.0	14.3	0.6	18.2	—	—	33.8	—	—

* Fluid removed and not returned to intestine.
† Fluid removed, measured, an aliquot taken and unused portion returned to the Intestine.
‡ Pressure was maintained at 20–25 cm of water. Temperature was maintained at 37–39 C.
§ Fluid removed from intestine and retained for analysis.

Results

The results of the *first* group of experiments in which short-term distention of the upper intestine was studied in a series of 8 dogs are shown in Table 1. At the time when the intestinal segment was initially created no fluid could be obstained in 4 of 8 dogs studied. In the dogs in which no fluid was initially collected none of the subsequent procedures caused any increase in fluid accumulations in the intestinal segment under study. In 2 of the 4 dogs which had fluid in the intestinal segment initially, there was a marked increase in fluid in the first and second hours after distention above that collected during the 1 hour control period without distention. In 2 of the 4 dogs which had fluid in the intestinal segment initially, dilation caused no further increase in fluid accumulation over that collected during the control period without distention. No obvious changes in the sodium or potassium concentrations of the intestinal secretion resulted from distention.

The results of long-term obstruction of the proximal small intestine observed in the second group of dogs are shown in Table 2. In spite of complete obstruction, the dogs continued to drink water. No intravenous infusions were required to maintain the dogs. Vomiting occurred in less than half of the dogs studied. The dogs appeared to be a little distress. At the termination of the experiment

TABLE 2. *The Effect of Long-term Obstruction and Distention of the Proximal Small Intestine (Group II)*

No.	Hours Obstructed	Initially Distended*	Ml fluid Collected	Na/mEq/L	K/mEq/L	Protein mg/ml
1	24	no	0	—	—	—
2	24	no	20	105	6.8	68
3	24	no	0	—	—	—
4	24	no	200	128.0	6.0	8.3
5	24	yes	0	—	—	—
6	24	yes	0	—	—	—
7	24	yes	0	—	—	—
8	24	yes	0	—	—	—
9	48	no	210	130	8.3	20.0
10	48	no	20	150	7.5	—
11	48	no	40	112	9.2	—
12	48	no	0	—	—	—
13	48	no	20	120	9.9	—
14	48	yes	0	—	—	—
15	48	yes	0	—	—	—
16	48	yes	0	—	—	—
17	48	yes	0	—	—	—
18	48	yes	0	—	—	—
19	72	no	80	130	8.8	8.3
20	72	no	90	159	9.9	68.2
21	72	yes	0	—	—	—
22	72	yes	0	—	—	—
23	96	no	90	159	9.9	68.2
24	96	yes	0	—	—	—

* Intestinal segment was distended with 50–60 cc of air

TABLE 3. *Effects of Obstruction and Distention on Fluid Accumulation in the Distal Small Intestine (Group III)*

Dog No.	Hours of Distention	Initially Distended	Fluid in Closed Hoop	Fluid above Proximal Occlusion (Ml)	Na (mEq/L)*	K (mEq/L)*	Intestinal Fluid Protein* (mg/ml)	Serum Protein (mg/ml)
1	72	no	0	20	152.0	11.1	27.5	—
2	72	no	0	100	132.5	25.1	55.6	—
3	72	yes	0	75	131.0	13.7	24.1	56.2
4	72	yes	0	200	146.0	17.6	38.7	57.4
Mean				98.7	140.3	16.8	36.4	56.8
± S.D.				75.3	10.2	6.1	14.1	—

* Concentration in intraluminal fluid above proximal obstruction.

when the peritoneal cavity was opened, there was no evidence of distention in any part of the intestine above or below the ligated segment. The amount of fluid recovered from the ligated intestinal segment is shown in Table 2. As indicated in the table, increasing the time of obstruction tended to increase the probability of finding fluid in the ligated intestinal segment. Mild distention with 60 ml of air, on the other hand, reduced the accumulation of fluid. There was no obvious relationship between the time of obstruction and the sodium and potassium concentrations of the intestinal juice.

The effects of obstruction and distention on fluid accumulation in the *distal* small intestine in the third group of experiments are shown in Table 3. The dogs of this group appeared to be more lethargic than those subjected to obstruction of the upper small intestine. They drank water and vomited occasionally. When the abdominal cavity was reopened, intestinal motility was observed to be present and became rather vigorous when the intestine was handled. There was no fluid accumulation in the closed loop segment of the intestine. As indicated in Table 3, however, 20–200 cm of fluid could be collected above the obstructed segment of intestine.

The intestine of the *fourth* group of dogs was examined after 24 hours and found to be practically empty. Neither the closed loops which had initially been filled with fluid nor those which were initially empty contained fluid at that time. Alternate intestinal loops were again refilled with 20–25 ml of saline. When the intestines were examined on the following day, they were again empty. There was no leakage of the blue dye into the loops which were not filled. The blue dextran was retained in the intestinal segments in which it had been injected. The dogs remained quite cheerful throughout the 48 hour period.

Discussion

Clinical observations[1,2,5,6,8,10,12,14,16–18] strongly supports the view that patients with intestinal obstruction become rapidly and progressively dehydrated and in electrolyte imbalance. This has also been observed in animals.[4,11] Toxic manifestations are seen as time progresses.[11]

Vomiting[1,6] has been reported as a major cause of dehydration and electrolyte imbalance in upper intestinal obstruction. Although vomiting is a major cause of dehydration in upper intestinal obstruction in the human, there have been relatively few comparable studies reported in dogs. In the current series of experiments involving upper bowel obstruction in 38 dogs, vomiting could be observed only in four. When vomiting was observed it was only a small amount, less than 100 ml. Shields[13] also observed that vomiting was rare in obstructed dogs.

It has been suggested[6,9] that intestinal distention can provide a strong stimulus for secretion which could in turn lead to dehydration. In experiments involving short-term distention of the intestine with air at 25 cm of water pressure no consistent effect on intestinal fluid accumulation was observed. In experiments involving distention of the intestine with air from 24 to 96 hours, no marked fluid accumulation occurred either within the obstructed segment or in the intestine above the obstructed segment. These observations are compatible with the findings of Wells[18] who reported that the absorption of a saline solution from closed loops in dogs was in direct proportion to the intraenteric pressure.

Previous investigators suggested that a significant part of the plasma volume could accumulate within the gastrointestinal tract. Moore[10] stated that 5–9 L of fluid may be sequestered into the distended intestine in humans during ileal obstruction. Drucker and Wright[2] stated that closed loop obstructions, particularly those involving a large part of the small bowel, resulted in a rapid transfer of intracellular fluid into the gut. Shields[13] found that in dogs water accumulated in the obstructed ileum at a rate of 13 ml per 10 minute period. The accumulation of large amounts of fluid within the intestinal lumen was not found in the current series of experiments. In 5 of the 8 dogs subjected to distention of the proximal small intestine practically no fluid could be recovered from a 60 cm intestinal segment after 2 hours. In experiments involving long-term obstruction of closed intestinal loops in the proximal small intestine in the current investigation, no fluid could be obtained in 15 of 24 dogs studied.

In experiments involving closed loop obstruction of the distal small intestine, no fluid could be obtained from the intestinal segments of any of the 4 dogs studied in this series of observations.

Enderlen and Hotz[3] noted the extravasation of fluid into the bowel occurred during the later stages of intestinal obstruction. In the current investigation in experiments involving upper bowel obstruction, it appeared that the number of dogs with fluid accumulation in their intestinal loops increased as obstruction was prolonged, provided the intestinal loops were not initially distended with air. In lower bowel obstruction there was no fluid accumulation even after 72 hours of obstruction.

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Radical Treatment of Recurrent Cystosarcoma Phylloides

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Malignant cystosarcoma phylloides is a rare breast cancer which frequently recurs locally before metastasizing. Local recurrence of cystosarcoma phylloides is unlike adenocarcinoma of the breast since it does not necessarily indicate systemic metastases; and, therefore, aggressive surgery can cure a number of patients with locally recurrent tumor. The present report is an extreme example of a patient with locally recurrent malignant cystosarcoma phylloides, and it illustrates the value of radical surgery in controlling this disease which had previously recurred 21 times. Fifteen months following sternal resection, the patient enjoys her longest tumor-free interval in 16 years.

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CYSTOSARCOMA PHYLLOIDES is a rare tumor comprising 0.3% to 0.9% of all breast tumors. The majority (70%) of these appear benign on histological examination. However, a significant number of "benign" tumors will recur and some have been reported to metastasize.[11,21] Even more confusing is the frequent propensity for the malignant variant of cystosarcoma phylloides to repeatedly recur locally before metastasizing. When the surgeon encounters such local recurrence, he often performs a conservative operation because of presumed coexistent metastatic disease. The result of such therapy is further local recurrences in addition to distant spread. The purpose of this report is to describe a radical surgical procedure to locally control a malignant cystosarcoma phylloides which had recurred 21 times.

Case Report

In 1958, a 50-year-old white female (NIH #09-51-49-3) underwent biopsy of a lump in the left breast which was reported to be cystosarcoma phylloides. Approximately one year later, the mass recurred and she underwent a simple mastectomy. The pathologic report was again cystosarcoma phylloides. She subsequently had 19 more recurrences in the anterior chest wall; each treated with local excisions. By 1970, the pathologic diagnosis was reported as malignant cystosarcoma phylloides. At that time, the patient received 2000 R to the anterior chest wall, following which the lesions recurred at an even faster rate with three recurrences developing in the 12 months prior to our examination.

In December 1972, she was referred to the Surgery Branch of the National Cancer Institute. Examination revealed a 4 × 5 cm mass on the anterior chest wall overlying the sternum at the level of the fourth rib, and this non-tender mass was fixed to the underlying tissue at the medial margin of the mastectomy scar (Fig. 1). There were no palpable axillary, supraclavicular or cervical lymph nodes, and the remainder of the physical examination was negative. Workup for metastatic disease (including chest tomograms, IVP, upper GI series, barium enema, and bone, brain, liver and gallium scans) was negative.

On the 21st hospital day, the patient underwent sternectomy from the level of the third rib to the xyphoid process, partial resection of ribs 4, 5, 6 and 7 on the left; excision of the previous mastectomy scar; and left axillary and bilateral internal mammary lymph node dissection. The sternal defect was closed with lyophilized fascia lata homograft, which was covered with a skin flap from the opposite breast. The remainder of the exposed chest wall was covered with split thickness skin graft. Postoperatively, she did well except for retraction of the breast flap, leaving a portion of the fascial homograft exposed. This was treated with saline soaks and procine heterograft coverage to stimulate granulation. Finally, the area was covered successfully with autogenous skin grafts. Pathologic diagnosis of the specimen, as well as all 20 previous recurrences, was malignant cystosarcoma phylloides. The tumor penetrated between the ribs, but did not invade the bone or pleura. Axillary and internal mammary lymph nodes were negative for tumor. The patient was discharged in good condition and at this time, 15 months following surgery, enjoys the longest recurrence-free interval she has experienced in the past 15 years (Fig. 2).

Discussion

Histologically, cystosarcoma phylloides is characterized by proliferation of both the stromal connective tissue and epthelial components. The malignant variety exhibits marked hypercellularity of the connective tissue stroma, with cellular atypia and frequent mitoses.[12] All of these features were present in the case reported (Fig. 3).

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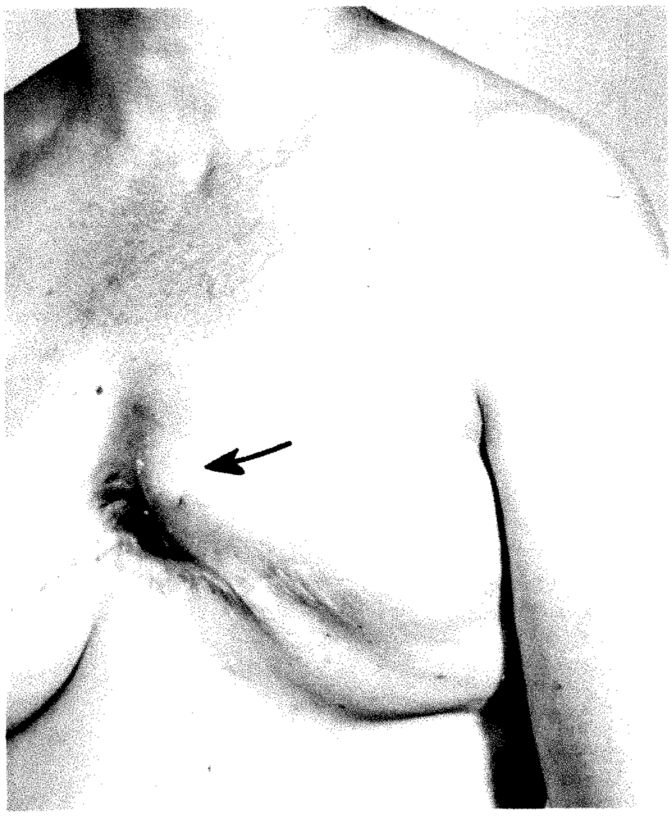

FIG. 1. Preoperative photograph of the patient showing the large 4 × 5 cm recurrence on the left anterior chest wall (arrow).

The clinical behavior of malignant cystosarcoma phylloides is well documented.[1,6,9,14,16] Metastases have been reported to occur in as few as 6.6%[20] of cases to as high as 70%.[11] The overall metastatic rate is approximately 25%. Most metastases are blood-borne but spread to axillary lymph nodes has been reported to comprise about 10% of all metastases.[10,13,15,19] Occasionally, direct invasion of the chest wall and lungs occurs.[17] Local recurrence is the single factor most associated with metastases. Kessinger[7] in her review of 59 patients with metastatic cystosarcoma phylloides found that 26 of these patients (44%) had a minimum of one local recurrence prior to metastasizing. However, local recurrence of cystosarcoma phylloides does not always indicate systemic metastases. Norris and Taylor reviewed 20 cases of malignant cystosarcoma phylloides and noted that while eight of these patients (40%) recurred locally, only five of the 20 (25%) metastasized.

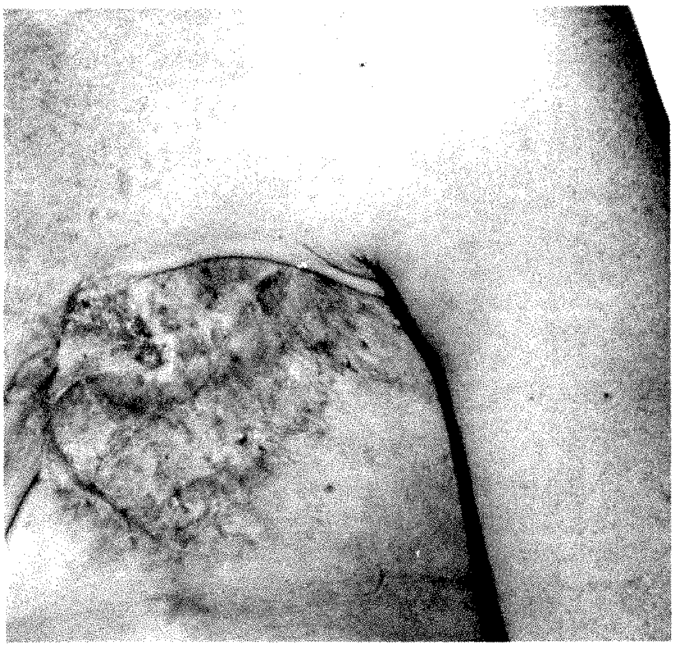

FIG. 2. Photograph of the patient nine months following surgery demonstrating the well-healed operative site.

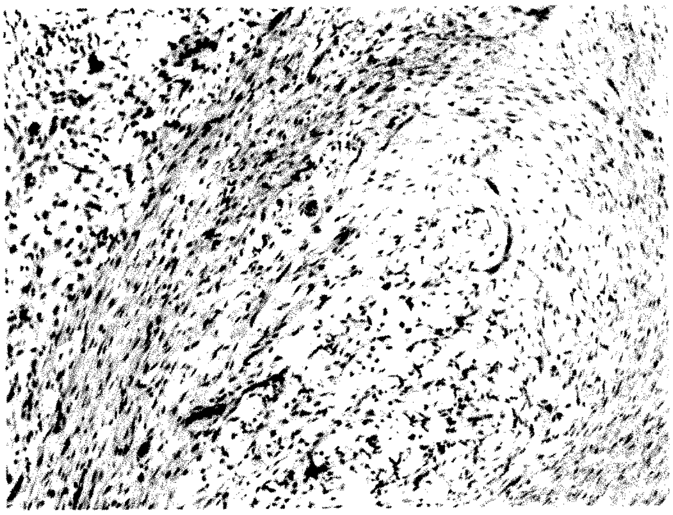

FIG. 3a. Photomicrograph of the original tumor removed in 1958. Note the marked hypercellularity of the connective tissue stroma and cellular atypia. (H & E ×140).

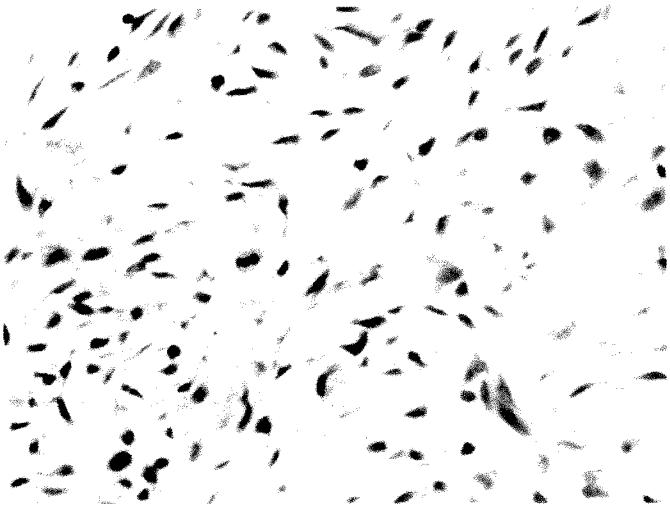

FIG. 3b. High power photomicrograph of the primary tumor showing bizarre cells with frequent mitoses characteristic of the malignant form of cystosarcoma phylloides. (H & E ×560).

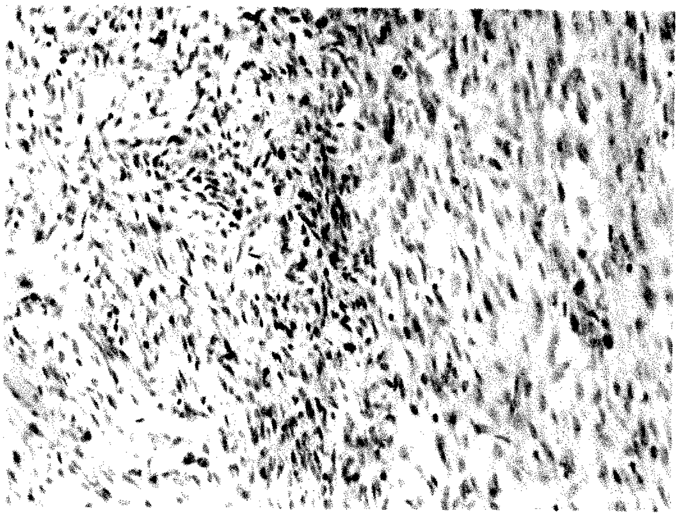

FIG. 3c. Low power photomicrograph of the 21st recurrence which demonstrates the proliferation of epithelial and stromal elements and cellular atypia previously seen in the primary tumor. (H & E 225×).

It appears, therefore, that control of the primary tumor is of paramount importance in successfully treating malignant cystosarcoma phylloides. Most authors[2,3,17,19] have recommended a minimum of simple mastectomy as the initial procedure for this disease. However, in marked contrast to adenocarcinoma of the breast, where local recurrence is metastatic spread,[4,5,8,18] recurrence in cystosarcoma phylloides is not necessarily a manifestation of systemic disease. Therefore, the patient presenting with local recurrence deserves aggressive surgery to control the local disease.

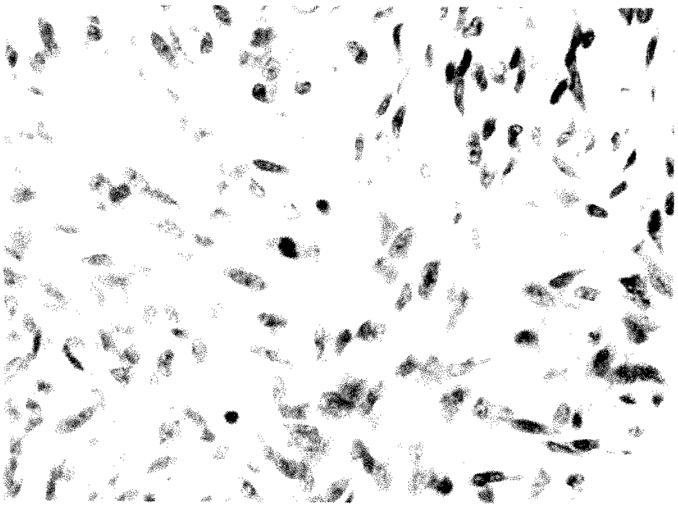

FIG. 3d. High power photomicrograph of the 21st recurrence. Immature nuclei and frequent mitoses are prominent features of this malignant tumor. (H & E 560×).

Our patient is an example of effective management of recurrent cystosarcoma phylloides by radical surgery. Despite the unusually high number of recurrences in this patient, an aggressive approach to recurrent malignant cystosarcoma phylloides was successful.

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Thyroid Carcinomas Arising in Thyroglossal Ducts

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Six cases of thyroid carcinoma arising in a thyroglossal duct cyst are described and combined with previously reported cases to provide a total of 66 cases for retrospective analysis. Most presented as benign thyroglossal duct cyst, and the malignant nature of the lesion was not recognized until the permanent pathology sections were reviewed. Eight of 10 patients with metastatic disease in retrospect had preoperative indications of malignancy as manifest by clinically suspicious nodes or a thyroglossal cyst larger than the mean for the series. The primary cell type in all cases was papillary thyroid carcinoma. Local resection by the Sistrunk method and suppressive doses of thyroid are recommended for the patient with papillary thyroid carcinoma arising in a thyroglossal duct cyst when there is no evidence of extension of the malignancy beyond the confines of the cyst. The patient presenting with metastatic carcinoma should, of course, be treated with appropriate local resection, hormonal manipulation, thyroid ablation, and lymphadenectomy as indicated by his age and sex, the cell type of the tumor, and the extent of local and metastatic disease.

THYROID CARCINOMA arising in a thyroglossal duct cyst is an unusual lesion and seldom suspected preoperatively. Most present as benign thyroglossal duct cysts and are not recognized as malignant until the permanent pathology specimens are reviewed. Much confusion often arises when such a lesion is encountered. This paper presents six cases of thyroid carcinoma of thyroglossal duct origin encountered during the review of over 600 cases of thyroid cancer from the United States Air Force Central Tumor Registry. It is our purpose to develop a rationale for the treatment of thyroglossal thyroid carcinoma from our experience and that extracted from the literature.

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Case Reports

S.P., a 43-year-old man, presented with a three-week history of an asymptomatic 1.5 cm infrahydoid midline neck mass which moved upward with protrusion of the tongue. Thyroid scan was normal. The lesion was preoperatively diagnosed as a thyroglossal duct cyst, and resection was carried out in the manner described by Sistrunk.[40] By gross examination this was a 3 cm cystic tumor with a nodular swelling at one end. Microscopically, the lesion proved to be a papillary thyroid carcinoma arising in the cyst wall adjacent to a fibrous stalk. One month postoperatively, total thyroidectomy was performed and serial microscopic sections disclosed no additional foci of thyroid carcinoma. Postoperative ^{131}I was administered to ablate residual thyroid tissue detected in the thyroid bed by scintiscan. The patient is clinically free of disease two years following the first operation.

P.Q., a 23-year-old oriental woman presented with a two-year history of a slowly enlarging right anterior cervical mass and a five month history of left cervical adenopathy. A 3 cm mass was palpable at the level of the hyoid bone to the right of the thyroid cartilage. Although cervical lymphadenopathy was present bilaterally, the thyroid was palpably normal. Thyroid scintiscan was normal and no uptake was demonstrable outside the thyroid bed. Excisional biopsy of the parahyoid neck mass disclosed metastatic follicular carcinoma of the thyroid, and a total thyroidectomy with bilateral modified neck dissection was performed. As an incidental finding, a small submental mass with a stalk leading to the hyoid was found and resected in continuity with the central portion of the hyoid bone. By gross inspection, the thyroid gland was soft and small without evidence of carcinoma on multiple sections. Histologically, the small submental midline mass proved to be a mixed papillary and follicular thyroid carcinoma arising in a thyroglossal duct cyst and the lymph nodes contained metastatic thyroid carcinoma on both sides of the neck. Residual functioning thyroid tissue demonstrable by scintiscan was ablated with ^{131}I, and the patient begun on thyroid replacement. The patient is free of demonstrable metastatic disease after four years.

G.A.H., a 25-year-old man, had a one-year history of a fluctuating submental midline mass which had been aspirated on one occasion. Scintiscan of the thyroid and ^{131}I uptake were nor-

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mal. A Sistrunk procedure was performed, and 3 cm cystic mass filled with tan to dark brown fluid was identified. Microscopically, papillary carcinoma of thyroglossal duct origin was identified. Suppressive doses of thyroid hormone were instituted, and the patient is clinically free of disease at seven years.

G.D., a 38-year-old woman, with a history of two previous resections of a right submaxillary cystic mass (11 years and again nine years prior to admission) presented with a slowly enlarging two centimeter mass in the right anterior digastric triangle. The remainder of the physical examination and thyroid scintiscan were normal. Neck exploration disclosed a thin-walled, multiloculated cyst, 3 cm in diameter and connected by a stalk to the hyoid bone. Microscopic examination showed papillary thyroid carcinoma arising in a thyroglossal duct cyst. Lymph nodes from the submental triangle were free of cancer; however, four months later, the patient presented with bilateral cervical adenopathy. Accordingly, total thyroidectomy and lymph node excision was performed, but no residual tumor was identified. Residual thyroid tissue apparent in the thyroid bed on scintiscan was ablated with ^{131}I and replacement doses of thyroid hormone were given. The patient is currently 12 years post-ablation and clinically free of disease.

K.A.H., a 30-year-old woman, presented with an eight-month history of a cystic midline neck mass which had enlarged during pregnancy but regressed after delivery. The remainder of the physical examination and thyroid scintiscan were normal. A 4 cm cystic mass removed by the Sistrunk technique proved to be papillary adenocarcinoma originating in a thyroglossal duct cyst. The patient was begun on suppressive thyroid therapy. Followup to four years has revealed no evidence of recurrent disease.

D.S., a 24-year-old woman, who nine years previously had had an infrahyoid thyroglossal duct cyst locally excised, presented with a submental neck mass. At operation, a cystic structure was removed in continuity with the central portion of the hyoid bone. Although no caudad extension of the cystic mass was apparent, a duct-like structure superior to the hyoid and deep to the myelohoid was discovered and removed. Histologic sections showed a mixed papillary and follicular carcinoma arising in a thyroglossal duct cyst. Thirteen months following her initial procedure biopsy of a clinically suspicious cervical node showed papillary thyroid carcinoma. The patient has been lost to followup.

Embryology and Normal Histology

During normal embryonic development the median thyroid anlage migrates caudad from the area of the foramen cecum, through the second branchial arch to its permanent location in the neck. This migration sets the stage for the development of a thyroglossal duct cyst. Normally, the stalk between the embryonic pharynx and thyroid ruptures and obliterates during the migration process. However, in an unknown number of cases, a solid cord of cells persists. This anomaly may remain unnoticed in the absence of cyst formation. If a cyst occurs, it is usually a midline mass which moves with swallowing and protrusion of the tongue. The cyst usually arises below but may be at the level of, or above, the hyoid bone. Those cysts which lie above the hyoid bone not infrequently bulge to one side of the midline and present in the submandibular triangle. Small accumulations of normal thyroid tissue may occur in the wall of a thyroglossal duct cyst in 1.6–40% of benign tracts.[8,35,41]

Combined Material

A literature survey to date disclosed 62 cases of thyroid carcinoma originating in a thyroglossal duct cysts.[1–7,10–13,15,16,18–23,25–29,33–36,41–43,45,46] Two cases described in our series (P.Q. and K.A.H.) were previously reported and are still living without evidence of disease.[23] Addition of the four new cases brings the total number of reports of thyroid carcinoma arising in a thyroglossal duct cyst to 66.

There is a slight female preponderance (4:3). The peak incidence for females occurs in the fourth decade, and for males, it occurs in the sixth decade.

All but five of the 66 cases presented as benign thyroglossal duct cysts (e.g., a painless, non-draining, subcutaneous neck mass in or near the midline and just caudad or cephalad to the hyoid bone). The average size was 3 cm (1.2–12 cm). The malignant nature of the lesion was seldom suspected preoperatively. Because a history of pain, sudden enlargement, hoarseness, weight loss, or airway compromise was extremely rare, the malignant nature of the lesion was seldom suspected preoperatively. Although the patient noted the mass ten days to 15 years before operation, it most commonly was noted to be present for longer than one year. One patient (P.A.Q.), who presented with cervical metastasis, had the thyroglossal duct tissue detected only at the time of thyroidectomy.

The operative procedure was not described in four of the cases from the literature, and the cancer was found incidentally at autopsy in one case (Table 1). One patient had a node biopsy followed by thyroidectomy, and a modified bilateral neck dissection (P.Q.). Sixty patients had a local excision with removal of the thyroglossal tissue and usually the midportion of the hyoid bone, and of

TABLE 1. *Operative Procedures*

1. Unknown Procedure (Or No Procedure)
(5 Patients)
4 Pts.—Procedure Not Reported
1 Pt.—Autopsy Incidental*
2. Initial Local Excision (Usually Sistrunk)
(54 Patients)

No Additional Operation (39 Patients)	Subsequent Procedures (15 Patients)	
	Thyroidectomy	—12*
	Node Biopsy	— 5
	Node Dissection	— 6

3. Initial Local Excision and Concurrent
(6 Patients)

Node Picking	1
Strap Muscles	1
Node Biopsy	2
Radical Neck	2

4. Other Procedure
1—Node Biopsy—Thyroidectomy*
Bilateral Modified Neck

* Thyroid glands available for Pathologic Evaluation.

these, 39 had no additional surgery. Of the remaining 21 patients, six had in addition to the Sistrunk procedure, a concurrent procedure: local node excision, one; resection of strap muscles, one; node biopsy, two; and radical neck dissection, two. Fifteen of the 60 patients underwent additional operations subsequent to the initial Sistrunk procedure consisting of: thyroidectomy, 12; node biopsy, 5 and limited node dissection, 6.

In most cases, the lesion grossly appeared to be a cyst filled with tan to brown fluid. Tumor excrescences which proved to be thyroid cancer on microscopic examination were usually visible on the gross specimen. Although four cases did have a follicular component, the primary cell type in all cases was papillary. Normal follicles were present near the neoplasm in all of our own cases and were specifically identified in 24 of the other 62 cases. Three of 15 thyroid glands examined histologically were reported to contain foci of papillary cancer (Table 2). Of the 18 patients who had lymph nodes examined histologically at some time during their course, 11 were thought to be clinically "positive" by the surgeon, but only seven actually had metastases documented microscopically. Lymph nodes were clinically "negative" in seven patients, but three proved to contain metastatic carcinoma. Two of the patients with histologically proved nodal metastases had cancer in the thyroid gland as well as in the nodes and the thyroglossal duct cyst.

Of the 10 patients with metastatic disease, five had metastases at or prior to the time of the initial operative procedure (Table 2). Interestingly, of these five patients, three had clinically suspicious nodes, and in three the primary mass was larger than the mean for the series. Five patients had metastatic disease diagnosed from nine days to 13 months subsequent to the initial operation. In two patients, metastases were discovered in the immediate postoperative period during additional "prophylactic" surgery. In three patients, biopsy of clinically "positive" lymph nodes disclosed the metastases.

Followup ranging from 27 days to 21 years, and a mean followup of almost five years is available for 57 patients. Of the five deaths reported, one was an operative death, and in no patient was death attributable to metastatic disease. However, followup is far too short and too incomplete to derive meaningful conclusions about survival.

Discussion

The biological activity of thyroid carcinoma arising from the thyroglossal duct appears to be similar in most respects to histologically identical neoplasia arising from the main gland. The higher incidence in women of thyroid carcinoma is less striking in this relatively small series of thyroid carcinoma arising from the thyroglossal ducts. One might expect earlier detection of carcinoma in this ectopic location, but the age of detection is similar to carcinoma arising in the thyroid.[47] One apparent biologic difference is, however, noted. Whereas approximately 40–50% of all patients presenting with carcinoma originating in the ectopic thyroid have tumor spread outside of the gland,[9,17,47,49] only seven of the 66 patients with cancer of the thyroglossal duct had metastatic disease documented at the time of initial surgery or in the immediate postoperative period. It is possible that the apparent difference is not a real one in that nodes were not routinely examined histologically because of the exposure and extent of dissection with the Sistrunk procedure.

Although some have proposed that thyroid carcinoma in a thyroglossal duct probably represents a metastatic lesion,[24,32] we share the theory of those favoring a primary origin.[7,23,33] Certainly normal thyroid tissue has been documented along the course of normal thyroglossal ducts[8,38,41,44] and was specifically mentioned in at least 30 of the 66 cases in this series. There is no reason to suspect that thyroid tissue in an ectopic location should demonstrate any less malignant potential than similar tissue within the thyroid gland. In addition, none of our three patients who had careful serial sections of the

TABLE 2. *Patients With Metastatic Disease***

Time of Diagnosis	Tissue	Age	Sex	Mass Size	Duration	Ref.
Initial	Node	23	F	4 cm	2 Yrs.*	23
Initial	Node	26	M	6 cm	8 Mo.*	7
Initial	Node	44	M	12 cm	3 Mo.	23
Initial	Gland	23	F	6 cm	"Yrs"	45
Initial	Nodes	33	F	10 cm	8 Yrs.*	16
9 Days	Glands & Nodes	55	F	3 cm	6 Yrs.†	23
2 Mos.	Gland & Nodes	40	F	4 cm	"yrs"	36
1 Yr.	Node	20	F	3 cm	1 Yr.*	10
1 Yr.	Node	24	F	3 cm	9 Yr.*	D.S.
13 Mos.	Nodes Lungs Liver	9	F	2.25 cm	7 Yrs.*	26

* Palpable nodes preop.

† Actual tumor size 2.25 cm.

15 thyroid glands were available for pathologic evaluation: 13 glands from thyroidectomy (Table 1); 1 gland from autopsy incidental (Table 1); and 1 gland from autopsy.[26] Although Keeling & Ochner did not specifically state that the thyroid gland contained no cancer it is assumed to be free of cancer since complete autopsy was obtained and metastatic cancer was described elsewhere.

thyroid gland had tumor within the thyroid, and only three patients of 15 from the combined series who had their thyroid examined histologically demonstrated tumor. Still more support for primary thyroglossal duct origin of thyroid cancer is the fact that one of our patients and four from the combined series had histologically normal thyroid glands in the face of node metastases.

Most of the cases in the literature were reported soon after discovery. Accordingly, definite recommendations for the management of thyroid carcinoma arising in a thyroglossal duct cyst cannot be based on currently available survival data. In addition, the optimal treatment of papillary thyroid carcinoma itself is a somewhat controversial issue. That some confusion exists regarding the optimal management of papillary thyroid cancer when it arises in a thyroglossal duct cyst is evident from the wide variety of treatments provided our six patients and those in the combined series. However, since it appears that the biologic potential of carcinoma arising in a thyroglossal duct cyst is very similar to that of histologically similar carcinoma originating in the thyroid, certain broad recommendations may be made for patient management by dividing the patients into two groups.

The first group, by far the larger, is composed of patients who present with a thyroglossal duct cyst without any indication that cancer exists until the permanent histologic sections are returned following a Sistrunk procedure. This set of circumstances is by far the most common. Once the diagnosis of papillary thyroid carcinoma arising in a thyroglossal duct cyst is made, one must confirm his original assessment that there is no palpable abnormality in the thyroid gland or in the cervical nodes and that the patient's chest roentgenogram is normal. If thyroid scintiscan demonstrates no abnormality, and if there is no evidence of extension of the tumor through the cyst wall, further operative intervention is probably not indicated. Suppressive doses of thyroid hormone should be administered[14] and the patient followed closely. This approach seems justified since intraglandular dissemination of thyroid carcinoma as described by Russell *et al.*[37] was not common in this series, only three of 15 patients having microscopic tumor found within their thyroid gland. Furthermore, the significance of microscopic thyroid carcinoma is uncertain. Nonpalpable metastatic disease which might be present in nodes at the time of initial operation is likely to remain localized and pursue a "benign" course for years, giving ample opportunity for definitive surgical removal when and if the nodes become palpable.[30,31,48,49] In short, local excision by the Sistrunk technique followed by suppressive doses of thyroid hormone, appears to be adequate treatment for thyroid carcinoma arising in a thyroglossal duct cyst if there is no evidence of spread beyond the confines of the cyst.

Patients presenting with metastatic disease comprise the second, smaller groups of patients. As previously indicated, preoperative suspicion of metastatic malignancy should exist. This group of patients usually present with palpable cervical lymphadenopathy, a thyroglossal duct cyst which is larger or of longer duration than the mean for the series, or with a relatively large intracystic tumor mass. The presence and the extent of metastatic disease should be determined at the initial operative procedure and appropriate local resection, thyroid ablation and lymphadenectomy performed as indicated by the patient's age and sex, the cell type of the tumor, and extent of local and metastatic disease. Medical management and followup should be as outlined above.

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Editorial:

The Team Concept in the Surgical Treatment of the Morbidly Obese

IT IS A REAL CAUSE FOR ALARM to receive reports from increasingly large number of surgeons that they are doing small intestinal bypass operations for the treatment of morbid obesity. These operations are done in Community Hospitals by surgeons who have adopted the attitude that anyone who can do a simple intestinal anastomosis is qualified to carry out the procedure. Nothing can be more removed from fact or more dangerous to the morbidly obese patient. Shunting operations for the morbidly obese are still in the realm of clinical investigation and should be carried out by a multi-disciplined team, interested and trained in the care of the many metabolic alterations produced by the reduced small intestinal absorptive area.

The responsibility for the care of these patients should be shared by a single surgical-medical unit. We have interviewed and examined over 1,000 morbidly obese patients, operated on over 400, and have had all patients investigated preoperatively following a detailed protocol. This protocol depends on interpretation of studies by, and consultation with, members of the Department of Medicine and its Sections of Cardiology, Gastroenterology, Endocrinology, Rheumatology, Hematology and Physical Medicine. The Department of Psychiatry supervises the psychological testing of all patients, as well as carrying out psychiatric evaluation. The Department of Biochemistry, whose continuing interest in both metabolic and vitamin assay studies are of great importance, contributes to our information. This group of patients, most of whom weigh 300 to 500 pounds, are best served by a Department of Anesthesia experienced in the conduct of anesthesia in the massively obese and alert to the management of intra-operative and post-operative problems. There is reason to believe that the mortality and major complication rates are more frequent in the "anybody can do an anastomosis" situation, than in Centers undertaking the treatment of the morbidly obese as a special clinical investigational program.

Finally, all members of the team should be alert to the real possibility of the development of hypokalemia, hypocalcemia, hypomagnesemia, renal stones, impaired hepatic function, and arthritis. They must be prepared to follow and treat these patients with intelligence and interest. Failure to adhere to a strict protocol of investigation and close, long-term follow-up is a disservice by the surgeon to the obese patient.

Gene B. Starkloff, M.D.
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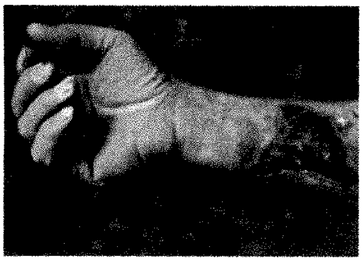

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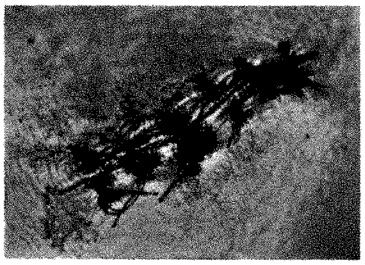

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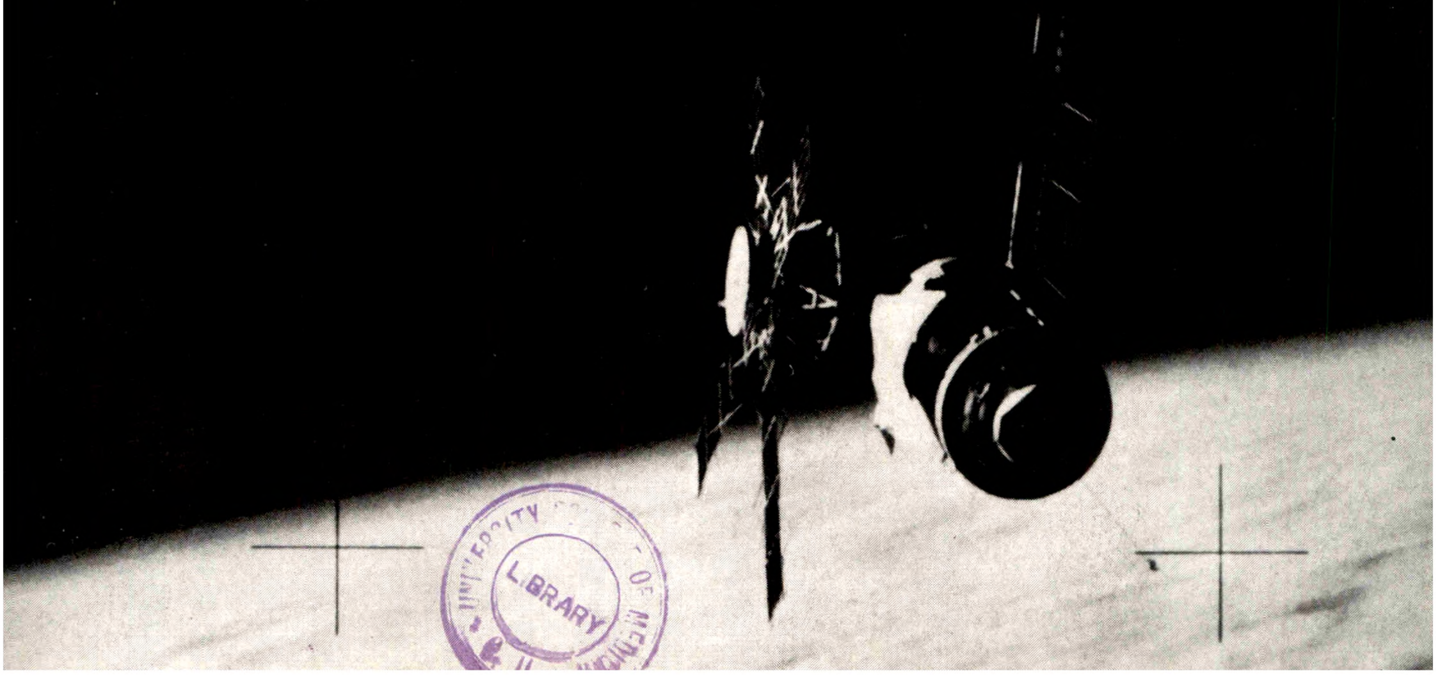

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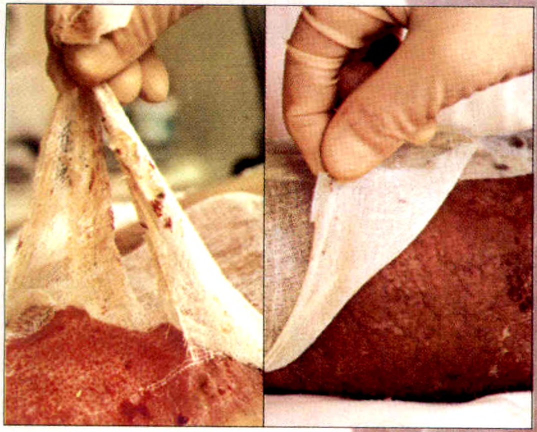

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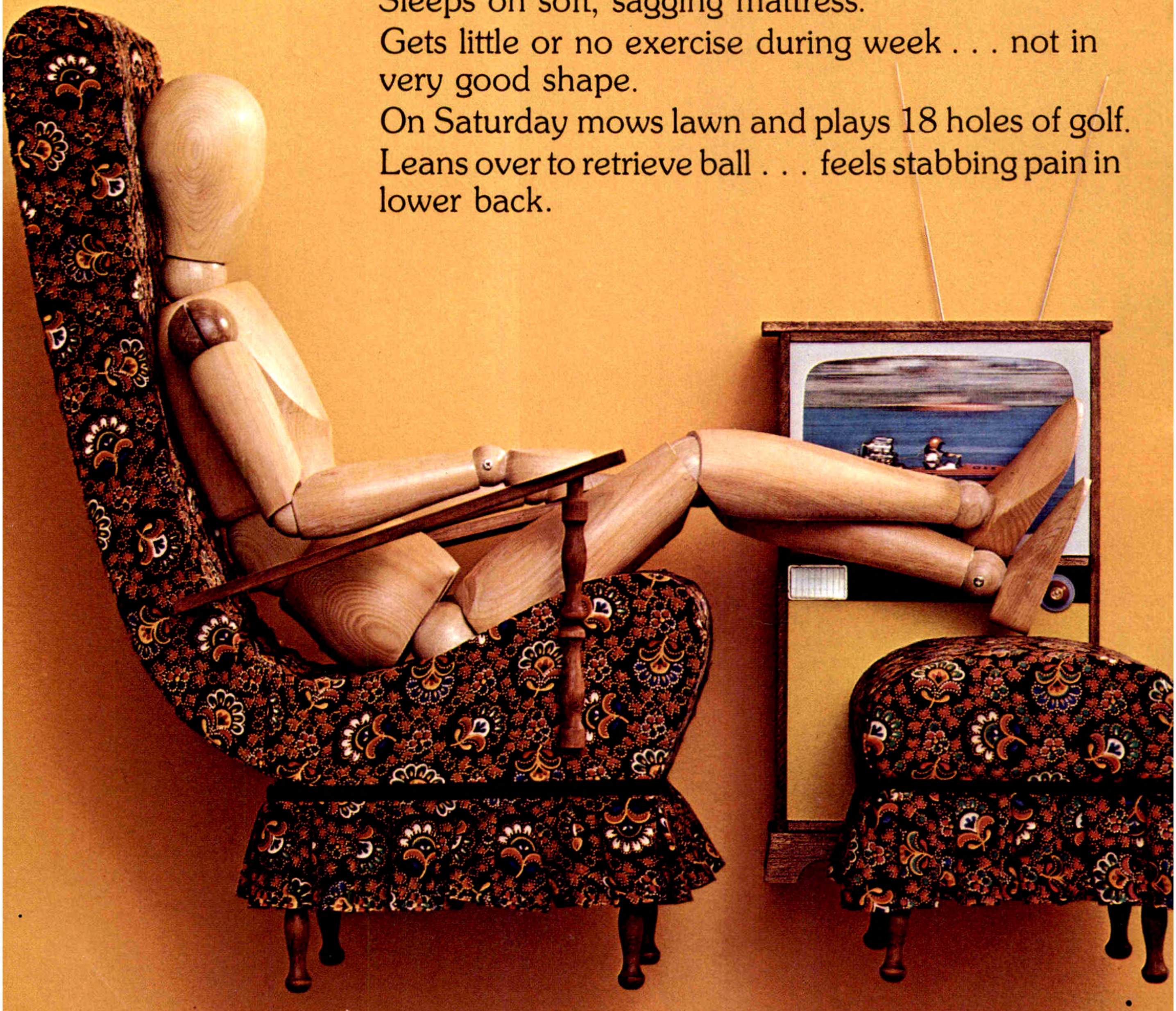

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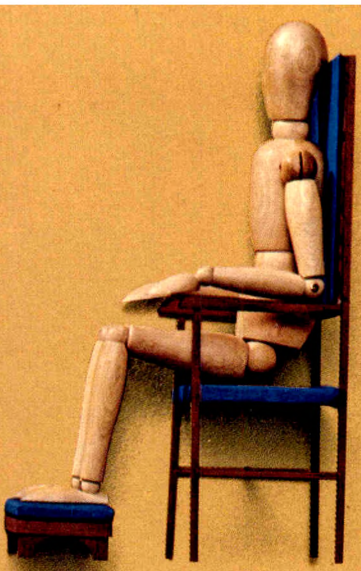

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Precautions:
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It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

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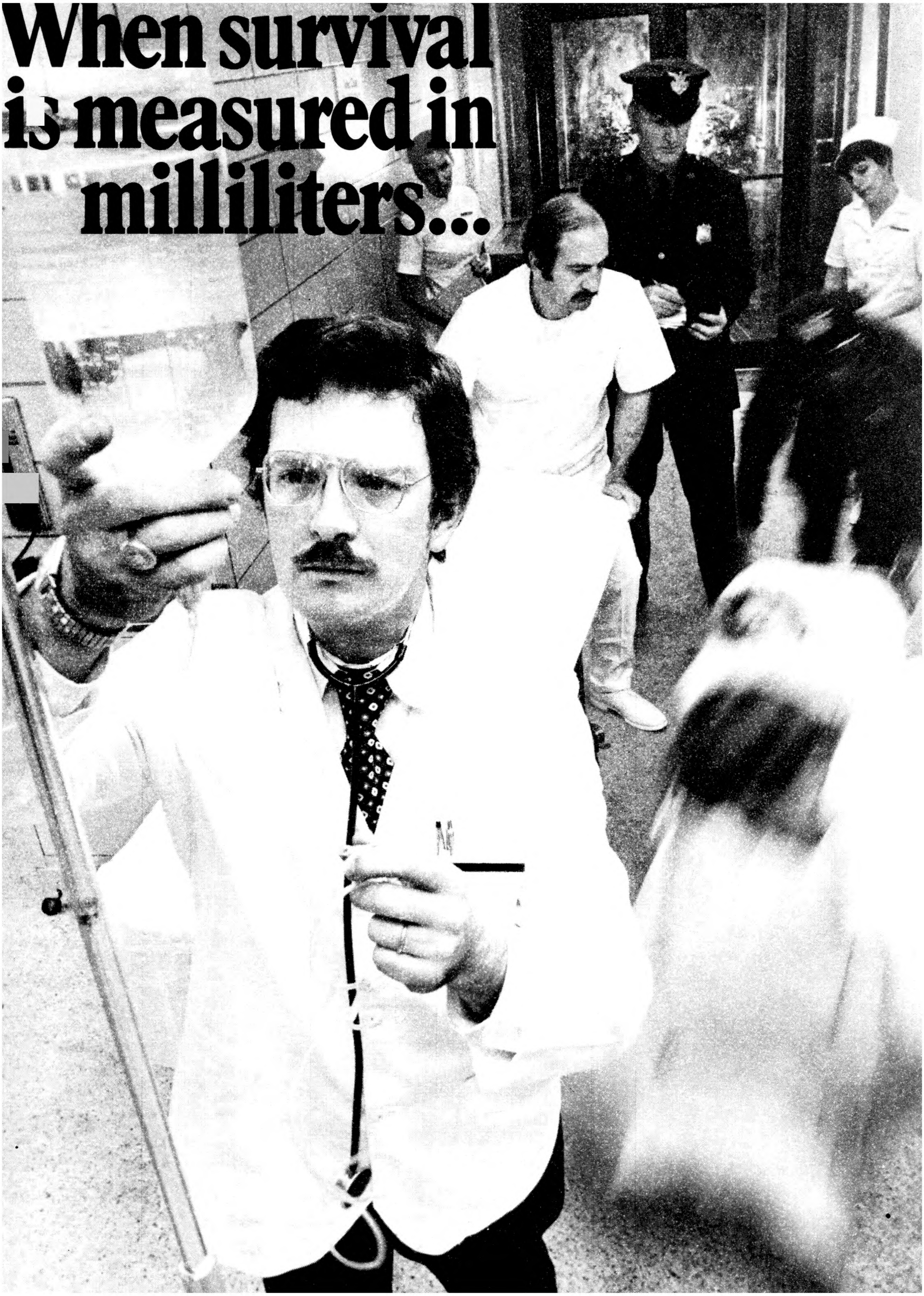
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Greater Initial Plasma Volume

In a recent study,[1] plasma volume expansion and cardiac output were measured in 36 patients with moderate or severe degrees of shock and in eight healthy subjects before, during and after infusion with 500 ml 10% dextran 40, whole blood, 6% dextran 70, plasma, and 5% dextran 40. The greatest plasma volume expansion was established in the 24 shock patients treated with Rheomacrodex. Peak plasma volume increases were more than one liter above controls. Plasma volumes decreased slowly as urinary output increased. Other studies also show the superiority of Rheomacrodex over blood, plasma, saline or lactated Ringer's for increasing initial plasma volume.[2-5]

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Measurement of hemodynamic effect revealed increased cardiac output directly related to increased volume expansion. Peak C.O. values occurred 15 minutes after Rheomacrodex infusion. In patients with moderate or severe degrees of shock, 10% dextran 40 increased cardiac output an average of 70% above control values.[1] Rheomacrodex improves hemodynamics—restores effective cardiac output and tissue perfusion—better than whole blood, plasma or clinical dextran.

Increased Tissue Perfusion

Restoring blood pressure often is not enough to reverse shock. Most important is the maintenance of adequate tissue perfusion. Rheomacrodex achieves this by decreasing red blood cell aggregation to a greater extent than crystalloids, blood or plasma.[6-10] This improvement in microcirculatory blood flow is reflected in increased oxygen availability and consumption, a vital contribution to the reversal of shock.[11]

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In hypovolemia, delayed renal clearance tends to prolong the colloid osmotic effects of Rheomacrodex.[1] During infusion, Rheomacrodex is evenly distributed in the vascular system. The plasma concentration of dextran fall rapidly during the first hour as smaller molecules are excreted. Generally, 70% of Rheomacrodex infused in normovolemic subjects is excreted via the kidney in 24 hours.[12] Excretion is then slowed as the higher molecul weight fraction of dextran remains in the circulation to b metabolized at the rate of 70-90 mg/kg body weight per 24 hours.

Guidelines for Use

1. May be administered on a "response to therapy basis" up to 1,500 ml initially in first 24 hours.
2. Infuse first 500 ml within 30 minutes.
3. To support blood volume beyond 24 hours, administer 500 to 1,000 ml daily.
4. Do not continue beyond five days.
5. May be given with whole blood.
6. Keep patient well hydrated. Increase hydration if urine flow drops below 50 ml/hour.
7. Can be given to any patient without blood typing. However, blood should be drawn prior to infusion for future testing.

REFERENCES: **1.** Shoemaker, W.C. and Monson, D.O.: Surg. Gynec. Obstet. 137:453, 1973. **2.** Ahnefeld, F.W. et al.: Anaesthesist 14:137 (May) 1965. **3.** Gelin, L.E. et al.: Acta Chir. Scand. 122:309, 1961. **4.** Gruber, U.F. et al.: Proc 10th Cong Int Soc Blood Transf., 1965, pp. 1116-1119, S. Karger, Basel (Switzerland). **5.** Gruber, U.F. et al.: Symposium on Rheomacrodex I (1964), pp. 13-23. **6.** Mainardi, L.C. et al.: Surgery 56:349 (Aug.) 1964. **7.** Martinovic, N. and Melrose, D.: J. Cardiovasc. Surg. 4:610 (Aug.) 1963. **8.** Suzuki, F. et al.: Ann. Surg. 160-263 (Aug.) 1964. **9.** Baker, R.J. et al.: Arch. Surg. 90:538 (Apr.) 1965. **10.** Baker, R.J. et al.: Arch. Surg. 89:373 (Aug.) 1954. **11.** Mohr, P.A. et al.: Circulation 39:379 (1969). **12.** Arturson, G. and Wallenius, G.: Scand. J. Clin. Lab. Invest. 16:81, 1964.

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PRECAUTIONS: Doses up to 15 ml/kg may produce small changes in coagulation; factor VIII may decrease markedly, but bleeding time is only rarely prolonged significantly. Observe all patients for early signs of bleeding complications. Monitoring of central venous pressure may help avoid circulatory overloading. Do not depress hematocrit below 30 vol. %. Dextran interference with blood glucose determinations, some blood typing and cross matching procedures and bilirubin and protein assays can be avoided by drawing blood samples pri giving Rheomacrodex or by informing lab that Rheomacrodex has been given so that suita assay methods can be used.

ADVERSE REACTIONS: Hypersensitivity reactions, which occur infrequently, can range fro mild cutaneous eruptions to generalized urticaria, nausea and vomiting, tightness of the ch wheezing, and, rarely, to anaphylactoid (allergic) shock. If any such reactions appear, start appropriate countermeasures promptly.

DOSAGE: Total dosage should not exceed 20 ml /kg in the first 24 hours or 10 ml /kg in eac subsequent 24 hours. Do not continue beyond 5 days.

SUPPLIED: Bottles of 500 ml 10% solution in normal saline or in 5% aqueous dextrose.

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ANNALS OF SURGERY

Vol. 180 December 1974 No. 6

The Allografted Parathyroid Gland:

Evaluation of Function in the Immunosuppressed Host

SAMUEL A. WELLS, JR., M.D., JAMES F. BURDICK, M.D.,[*]
BRACK G. HATTLER, M.D.,[‡] CHRISTINE CHRISTIANSEN, B.S.,
HUGH M. PETTIGREW, Ph.D.,[§] MINOURA ABE, M.D.,[†] LOUIS M. SHERWOOD, M.D.[†]

Parathyroid autografts were performed in 19 random bred mongrels and parathyroid allografts were exchanged between seven random bred mongrels. Three pairs of siblings from a beagle colony were immunosuppressed and parathyroid allografts exchanged between them. The parathyroid autografts were successful, while parathyroid allografts failed on all occasions in the non-immunosuppressed host. In immunosuppressed animals, however, the allografts were successful in five of six dogs. The success of parathyroid transplantation was determined by the following observations: 1) The experimental animal, having grafted parathyroid tissue as the only source of hormone, maintained a normal or near normal serum calcium concentration. 2) Following removal of the parathyroid graft, there was an immediate fall in the serum calcium concentration associated with tetany and/or death. 3) Histological study of the grafted gland revealed normal architecture, and 4) Radioimmunoassay of extracted grafts revealed moderate to large quantities of parathyroid hormone.

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National Institutes of Health, Bethesda,
Maryland, and the Department of Medicine,
Michael Reese Medical Center, Chicago, Illinois*

WE HAVE RECENTLY DEMONSTRATED[15] that dogs having intramuscular parathyroid autografts as the only source of parathyroid hormone (PTH) maintain a normal or near normal serum calcium concentration. Following removal of the grafted parathyroid tissue, a significant fall in the serum calcium concentration occurs which is associated with tetany and/or death. Histological examination of the removed parathyroid autografts shows anatomically intact parathyroid architecture and the transplanted pieces contain high concentrations of PTH as demonstrated by radioimmunoassay.

The present report compares the function of transplanted parathyroid glands as autografts and as allografts in the immunosuppressed and non-immunosuppressed host.

Materials and Methods

Parathyroid Autotransplants

Nineteen random bred mongrels weighing 15–20 kg were anesthetized with Nembutal (27 mg/kg), intubated and maintained on halothane. For autotransplantation, three parathyroid glands, two upper and one lower, were removed and placed in Waymouth's medium at 4C. After the glands had become firm with chilling, each was cleaned and sectioned into four to six pieces, measuring approximately 1.5 × 0.5 mm. Each slender piece was then buried in a separate place within the fibers of the external oblique muscle. The overlying fascia of each implantation site was closed with a marking suture of fine silk. Every attempt was made to maintain complete hemostasis and sterility. The skin incisions were protected with sterile adhesive drape and skin towels. The incisions were closed in two layers and the skin was then sprayed with Aeroplast

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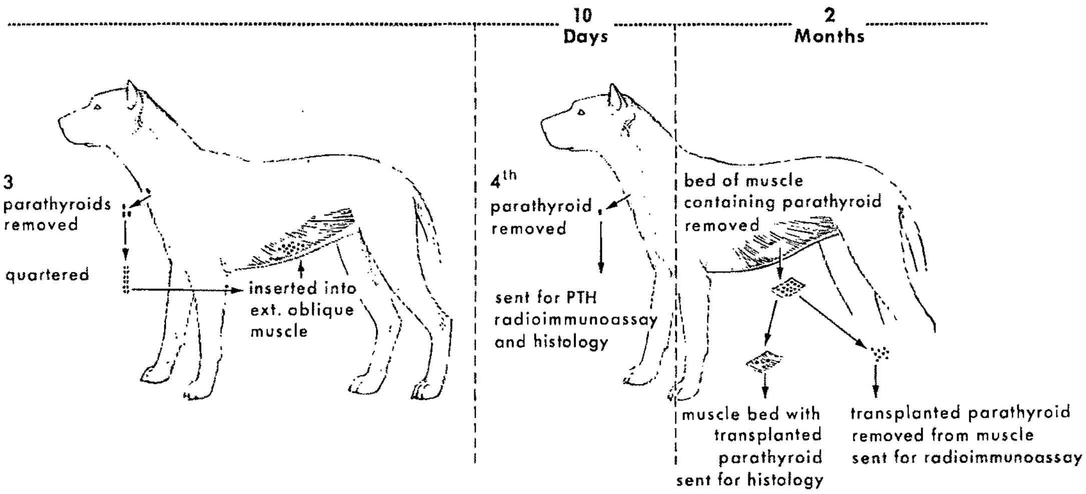
10 Days
2 Months
3 parathyroids removed
quartered
inserted into ext. oblique muscle
4th parathyroid removed
sent for PTH radioimmunoassay and histology
bed of muscle containing parathyroid removed
muscle bed with transplanted parathyroid sent for histology
transplanted parathyroid removed from muscle sent for radioimmunoassay

Fig. 1. Technique for parathyroid autografting in a random bred mongrel.

(Parke-Davis and Company, Detroit, Michigan). Postoperatively, all dogs received penicillin and streptomycin intramuscularly.

Ten days after grafting, each dog had its remaining *in situ* parathyroid gland removed from the neck. The lower halves of the thyroid lobes were also removed as this is a frequent site of accessory parathyroid tissue. At 60 days, the muscle beds containing the autografted parathyroid glands were removed and immediately placed in 4C saline. With the aid of a dissection microscope, several (six to eight) of the parathyroid grafts were removed from the muscle, immediately frozen on dry ice, and then stored in liquid nitrogen at −190 C for subsequent radioimmunoassay. The autografted pieces remaining in the muscle bed were fixed in formalin for subsequent histological study. The experimental design of the parathyroid autograft technique is graphically depicted in Fig. 1.

Parathyroid Allografts

Seven random bred mongrels weighing 15–20 kg were anesthetized as described above. Three parathyroid glands were removed from each dog and then chilled and sectioned into small pieces as described previously. These parathyroid grafts were then allotransplanted to the external oblique muscle of one of the other six dogs in the group. The method of muscle implantation was as described for the autografted dogs. Ten days after allografting, each dog had the remaining *in situ* parathyroid gland removed and four to five days thereafter all of these animals developed tetany. On the fourteenth day following allografting, all seven dogs had their muscle beds containing the parathyroid transplants removed. Some parathyroid pieces were removed and frozen for PTH radioimmunoassay while others were left in the muscle bed for histologic study.

Parathyroid Allografts in the Immunosuppressed Host

For these experiments three sibling pairs obtained from a beagle colony were used. The immunosuppression regimen consisted of rabbit anti-dog thymocyte globulin[°] (2 mg/kg, subcutaneously every other day for ten days beginning two days before allografting), methylprednisolone (2 mg/kg/day for two days, 1 mg/kg/day for two days and 0.5 mg/kg/day for two days, beginning on the day of allografting), and azathioprine (3 mg/kg/day beginning two days prior to allografting and continued throughout the course of the experiment). Acute graft rejection in this group, defined by a sudden drop in the serum calcium concentration below 7 mg/100 ml was treated with 500 mg of methylprednisolone i.v. daily for three days. After histocompatibility typing (see below) parathyroid allografts were exchanged between sibling pairs by the same technique described for the parathyroid allografts in the non-immunosuppressed hosts. Following removal of the remaining *in situ* parathyroid gland on day ten, the course of five of these six dogs closely paralleled that of the dogs receiving parathyroid autografts and therefore the muscle beds were not removed until day 60. At that time, parathyroid transplants were dissected out and frozen for PTH determination while other pieces remaining in the muscle were studied histologically. The technique of allografting the parathyroid glands in the immunosuppressed hosts is depicted in Fig. 2.

Diet

Throughout the experiment all dogs were maintained on dry dog chow (NIH-11-110 containing 2.1% calcium and 1.3% phosphorus).

Calcium Determination

Blood for analysis was drawn from a non-occluded vein and serum calcium was determined on the autoanalyzer by the method of Kessler and Wolfman.[9] Calciums were determined daily or every other day on all dogs.

[°] Prepared by Robert C. Davis, M.D., University Hospital, Boston, Massachusetts.

Radioimmunoassay of Transplanted Parathyroid Glands for Parathyroid Hormone

The PTH content of the frozen parathyroid transplants from each dog was determined by radioimmunoassay after extraction of tissue with a solution of 8M urea, 0.2N HCL and 0.14M β-mercaptoethanol at 4C for 12 hours. Aliquots of extracted tissue after centrifugation were added to the radioimmunoassay containing labelled bovine PTH and antibodies to bovine PTH. Appropriate controls for the extracting solution were utilized. Extracts of canine parathyroid tissue displaced labelled bovine PTH from binding to its antiserum with a slope parallel to bovine PTH (Fig. 3). Gland content of PTH could, therefore, be expressed in terms of nanograms of PTH (bovine equivalent) per milligram of tissue protein.[12] In our experiments the hormone content of the grafted parathyroid tissue was compared to the PTH concentration in fresh parathyroid glands and expressed as a percentage thereof.

Mixed Lymphocyte Culture Testing and Histocompatibility Typing of Beagle Pairs

Lymphocytes were obtained by passing heparinized whole blood over glass beads, diluting it 1:3 in RPMI-1640 solution and layering it on a 2.4:1 ficol-sodium diatrozoate mixture. After centrifugation at 450 g for 30 minutes, lymphocytes were obtained at the interphase which were greater than 70% pure. The remainder of the cells were monocytes and granulocytes. There was a 95% viability, determined by trypan blue exclusion. For mixed lymphocyte interactions, culture medium consisted of RPMI-1640 augmented with 1% glutamine (200 mM/ml), 0.5% penicillin, streptomycin (5000 units/ml), 0.5% heparin (1000 units/ml), and 15% fresh normal dog plasma. All experiments were carried out with 100,000 responding and 100,000 stimulating cells contained within a 0.2 ml culture volume using a micro-system. Stimulating cell suspensions were X-irradiated with 1,500 r. using a gamma cell Cobalt source. This irradiation prevented canine lymphocyte proliferation in MLC but caused no significant decrease in cell viability when tested by trypan blue exclusion. All cultures were prepared in quintuplicate and incubated for seven days in a 5% CO_2 and air mixture with 85% humidity at 37C. Litter mates were tested in all combinations as both responding and stimulating cells. Controls performed during each culture period consisted of lymphocytes from each animal cultured with X-irradiated autologous lymphocytes. Sixteen hours before the end of incubation, 20 lambda pulses of ^{3}H-thymidine, 20 µc/ml (specific activity 2 c/mM were added). At the time of culture termination, the cells were harvested on a microharvester and washed thoroughly with balanced salt solution. The strips of fiberglass filter paper were then dried in an oven at 180 C and added to 2, 5 diphenyloxazole toluene as scintillation fluid. Radioactive uptake was quantitated in CPM in a Packard liquid scintillation counter. As the same external standard was used each time no correction for quenching was necessary. Histocompatibility typing was carried out by a modification of the cytotoxicity test performed by Amos *et al.*[2] with a battery of antisera prepared in beagle dogs and defining various DL-A specificities. Of the six beagle dogs typed, two of the siblings were DL-A identical (B-17, B-21), two of the siblings

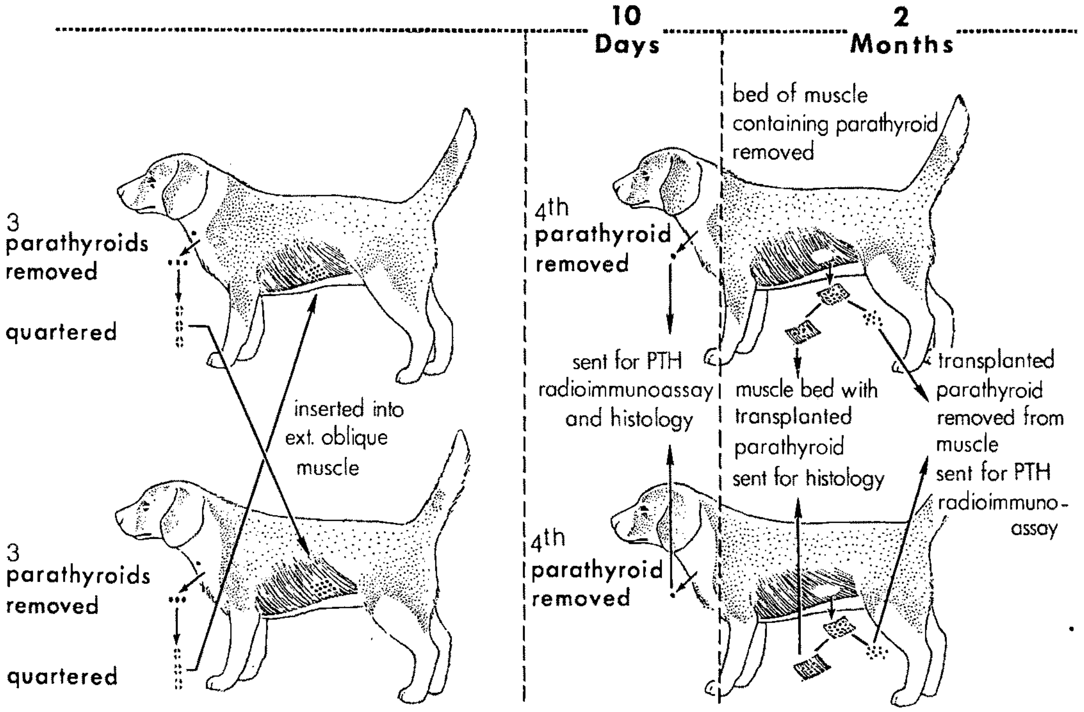
10 Days
2 Months
bed of muscle containing parathyroid removed
3 parathyroids removed
quartered
4th parathyroid removed
inserted into ext. oblique muscle
sent for PTH radioimmunoassay and histology
muscle bed with transplanted parathyroid sent for histology
transplanted parathyroid removed from muscle sent for PTH radioimmuno-assay
3 parathyroids removed
4th parathyroid removed
quartered

Fig. 2. Technique for parathyroid allografting in immunosuppressed beagle siblings.

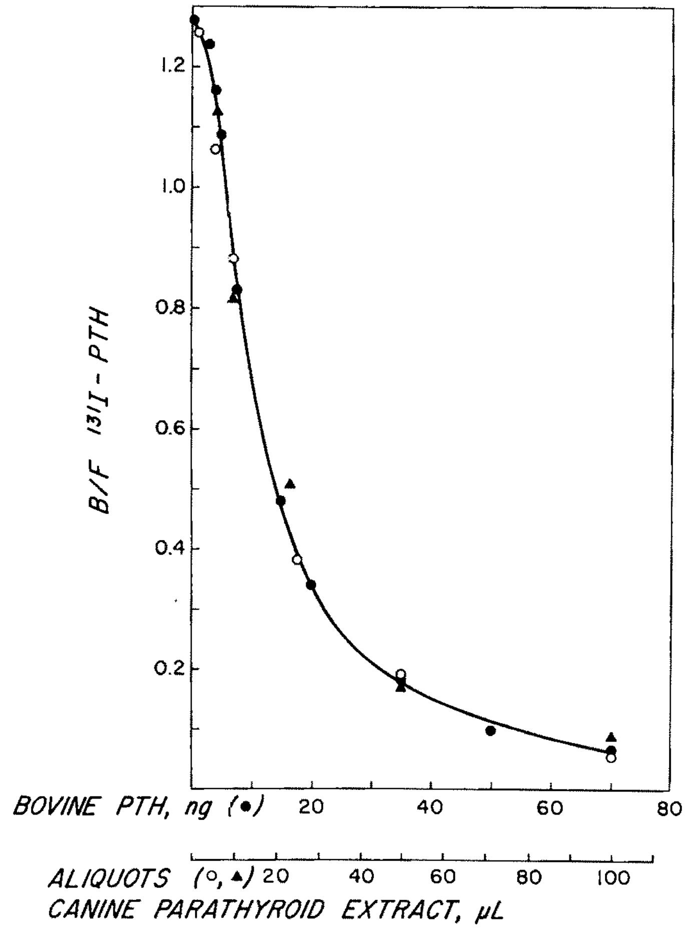

Fig. 3. Radioimmunoassay curve using labelled bovine PTH and antibodies to bovine PTH. Ratio of bound to free labelled hormone (B/F) is plotted against increasing concentrations of bovine PTH in canine gland extract. Parallel displacement by bovine and canine hormone is demonstrated.

showed a one haplotype difference (B-18, B20), and two siblings showed a two haplotype difference (B-26, B-27). Results of the mixed lymphocyte cultures conformed to the DL-A analysis.

Rabbit Antidog Antilymphocyte Globulin (ALG)

ALG was prepared by injecting groups of 7–10 New Zealand white rabbits with 1 × 10^9 dog thymocytes emulsified in Freund's complete adjuvant. Some 2–4 weeks following the initial immunization the rabbits received an intravenous booster injection of 1 × 10^9 thymocytes. One week later the rabbits were exsanguinated by cardiac puncture. The serum obtained was centrifuged twice to remove cells and Millipore filtered. The globulin fraction was obtained by three precipitations with 33 1/3% saturated ammonium sulfate. This globulin fraction was clarified by ultracentrifugation at 112,000 × g for two hours, passed through a Millipore filter of 0.45 micron, adjusted to 35 mg of protein/ml in phosphate buffered saline and placed in single dose bottles with a Merthiolate concentration of 0.01%. The resulting preparations were approximately 90% gamma globulin and 10% beta globulin. Thymocyte agglutination titers ranged from 1:256 to 1:512.

Statistics

Calcium concentrations at different intervals are compared using paired t-tests.[13] Parathyroid hormone content in transplanted glands is expressed as a percentage of that present in fresh tissues. Ninety-five per cent fiducial intervals were constructed[3] as shown in Fig. 4.

Histology

All tissue samples removed were fixed in 10% formalin, sectioned, and stained with hematoxylin and eosin.

Results

Parathyroid Allografts in the Non-immunosuppressed Host

The mean preoperative serum calcium concentration of the seven allografted dogs preoperatively was 10.3 ± 0.1 mg/100 ml (Table 1). Prior to the removal on day ten of the remaining gland from the neck, the mean serum calcium concentration had fallen slightly to 9.8 ± 0.3 mg/100 ml. Within four days after the remaining single parathyroid gland was removed, the mean serum calcium concentration

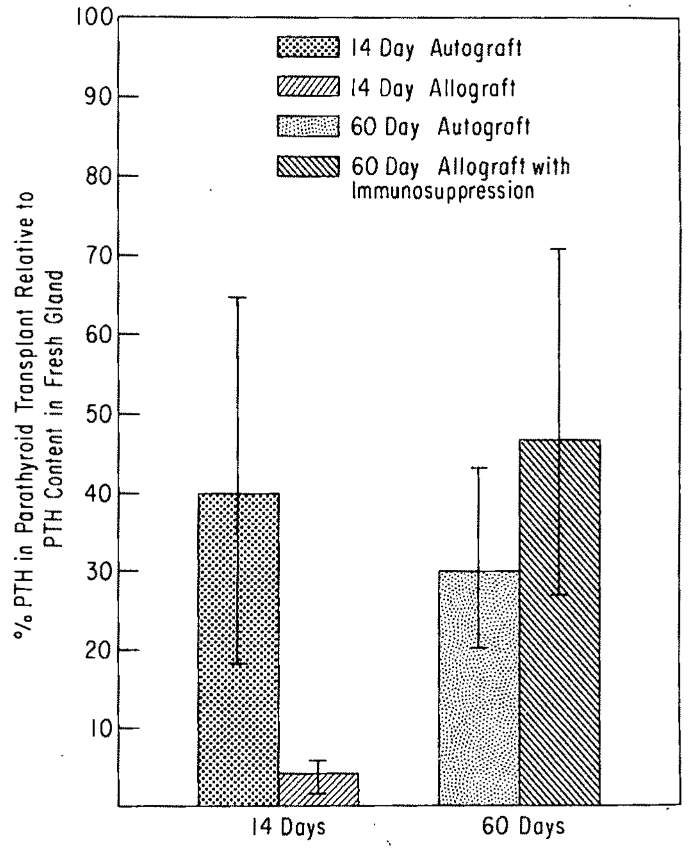

Fig. 4. Parathyroid hormone content in 14-day and 60-day parathyroid transplants, expressed as a percentage of hormone present in fresh parathyroid tissue.

TABLE 1. *Mean Serum Calcium Concentration in MGM/100 ± SEM*

	Day −1	Day 10	Day 14	Day 60	Day 70
Parathyroid Autograft	10.0 ± 0.2 (19)	9.3 ± 0.4 (6)	7.7 ± 0.3 (16)†	9.0 ± 0.2 (14)	5.2 ± 0.3 (14)‡
Parathyroid Allograft	10.3 ± 0.1 (7)	9.8 ± 0.8 (6)	4.6 ± 0.1 (7)†		
Parathyroid Allograft	9.9 ± 0.1 (6)	9.2 ± 0.2 (6)	8.2 ± 0.6 (6)°	9.6 ± 0.5 (6)	6.8 ± 0.2 (6)‡

Day −1 = Preoperative baseline mean serum calcium concentration.
Day 10 = Mean serum calcium concentration with one *in situ* parathyroid gland remaining.
Day 14 = Mean serum calcium concentration four days after the single remaining *in situ* parathyroid gland was removed.
Day 60 = Mean serum calcium concentration 60 days after parathyroid transplant.
Day 70 = Mean serum calcium concentration 10 days after grafted parathyroid tissue removed.
( ) = Number of dogs sampled.
° $p < 0.05$ mean serum calcium concentration on day −1 compared to mean serum calcium concentration on day 14.
† $p < 0.001$ (mean serum calcium concentration on day −1 compared to mean serum calcium concentration on day 14).
‡ $p < 0.001$ (mean serum calcium concentration on day 70 compared to mean serum calcium concentration on day 60).

had dropped to 4.6 ± 0.1 mg/ 100 ml (compared to the preoperative baseline serum calcium concentration the difference is highly significant, $p < 0.001$), and all dogs were in tetany but ambulatory. The external oblique muscle containing the parathyroid allografts was removed from each dog at this time. The mean PTH content of the removed parathyroid allografts was 3.7% of that present in fresh intact parathyroid tissue (Fig. 4). Histologically the parathyroid allografts were unrecognizable as parathyroid tissue, the architecture having been destroyed by mononuclear cell infiltration and by a tissue reaction characteristic of acute graft rejection (Fig. 5b).

Parathyroid Autografts

Nineteen mongrels received their own parathyroid glands as autografts. The mean serum calcium concentration of the group prior to transplantation was 10.0 ± 0.2 mg/100 ml. At day ten, just prior to removal of the last *in situ* parathyroid gland from the neck, the mean serum calcium concentration in six of the autografted dogs was 9.3 ± 0.4 mg/100 ml. Four days following removal of the remaining *in situ* parathyroid gland from the neck, the mean serum calcium concentration in 16 of the autografted dogs was 7.7 ± 0.3 mg/100 ml. Compared with their preoperative serum calcium concentration, this difference was highly significant ($p < 0.001$).

Because the PTH content of the removed parathyroid allografts had been so low (3.7% of that present in intact parathyroid glands), one might argue that the transplants had not had time to develop adequate vascularity and that the low PTH content was only a function of their poor nutrition. Therefore, five dogs which had received parathyroid autografts had their muscle beds containing the transplants removed at the same time as the parathyroid allografts had been resected. The PTH content in the removed parathyroid autografts was 39.1% of that present in fresh parathyroid tissue.

Furthermore, the parathyroid autografts removed at two weeks appeared normal histologically (Fig. 5c). The 14 remaining dogs who had received parathyroid autografts were followed for 60 days from the time of transplantation. The mean serum calcium concentration at this time was 9.0 ± 0.2 mg/100 ml. This value is within the normal range, and all animals appeared normal and were without signs of tetany. Each dog had its muscle bed containing the autografted parathyroid tissue removed electively at this time. The PTH content by radioimmunoassay in the removed parathyroid tissue was 29.7% of that present in intact fresh parathyroid tissue. Histologically the parathyroid autografts at two months appeared as normal parathyroid tissue (Fig. 5d). Within ten days after the parathyroid autografts had been removed, the mean serum calcium concentration in the 14 animals had fallen to 5.2 ± 0.3 mg/100 ml, a highly significant drop ($p < 0.001$) compared to the serum calcium concentration prior to graft removal.

Parathyroid Allografts in the Immunosuppressed Host

Parathyroid grafts were exchanged between three pairs of immunosuppressed beagle siblings by the same technique described for the previous allografts. The mean preoperative serum calcium concentration of the six dogs was 9.9 ± 0.1 mg/100 ml. At day ten, before the remaining *in situ* parathyroid gland had been removed from the neck, the serum calcium concentration was 9.2 ± 0.2 mg/100 ml. Four days following removal of the remaining neck parathyroid gland, the mean serum calcium concentration had fallen to 8.2 ± 0.6, a significant drop when compared to the preoperative calcium value ($p < 0.05$). All six of the immunosuppressed allografted beagles were then followed for 60 days. At this time the mean serum calcium concentration was 9.6 ± 0.5 mg/100 ml. The muscle beds containing the allografted parathyroid glands were then removed from the immunosuppressed animals and within ten days the mean serum calcium concentration had fallen to 6.8 ± 0.2, ($p < 0.001$). The PTH content of the removed parathyroid allografts was 46.9% of that present in fresh parathyroid tissue.

In four of the immunosuppressed allografted beagles (B-21, B-20, B-27 and B-26) there was no evidence of graft rejection on azathioprine maintenance. In two instances, (B-27 and B-26), methylprednisolone was used transiently for immunosuppression instead of azathioprine because the

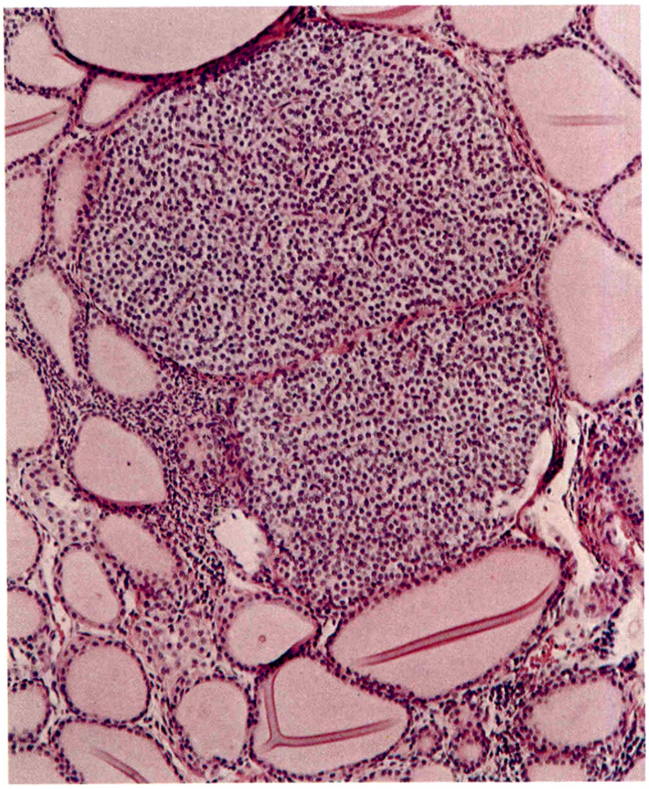

FIG. 5a

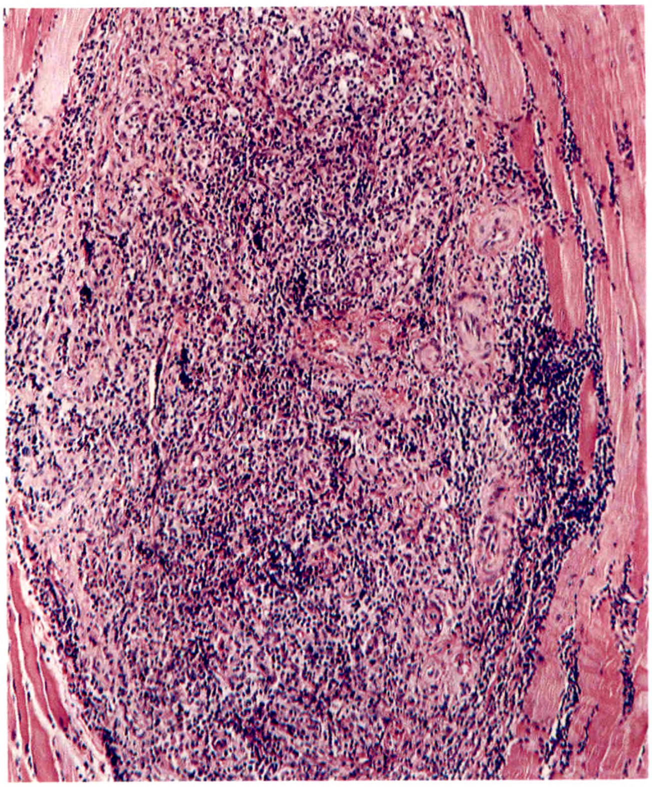

FIG. 5b

FIG. 5a. Normal canine parathyroid gland (hematoxylin and eosin × 100). FIG. 5b. Allografted parathyroid gland removed from a non-immunosuppressed host at 14 days. Note massive infiltration of mononuclear cells and destruction of parathyroid gland architecture (hematoxylin and eosin × 100). FIG. 5c. Parathyroid autograft removed from muscle bed at two weeks (hematoxylin and eosin × 125). FIG. 5d. Parathyroid autograft removed at 60 days (hematoxylin and eosin × 100). FIG. 5e. Parathyroid allograft from dog B-20 removed at 60 days (hematoxylin and eosin × 100). FIG. 5f. Parathyroid gland removed from dog B-18 at day 60. Note patchy infiltration of mononuclear cells and otherwise normal parathyroid architecture (hematoxylin and eosin × 100) *Color photographs were made possible through a grant from the Albert and Eunice Currie Memorial Fund.*

white blood cell count had dropped below 3500 in these animals. The courses of two of these dogs (B-26 and B-20) are depicted in Figs. 6a and 6b. The parathyroid allograft removed at day 70 in Dog B-20 is shown in Fig. 5e.

Dog B-18 maintained a normal serum calcium concentration on azathioprine immunosuppression until day 50. At that time, there was an acute drop in calcium concentration to 6.9 mg/100 ml. The animal was treated with methylprednisolone 500 mg/kg for three days. The calcium concentration increased to 8.7 mg/100 ml and five days later (day 60) the parathyroid allograft was removed. The clinical course of this animal is depicted in Fig. 6c and the removed parathyroid allograft in Fig. 5f.

Dog B-17 never developed a normal serum calcium concentration after allotransplantation. This dog was treated intermittently with calcium gluconate injections and large doses of methylprednisolone in an attempt to reverse the apparent immunologic rejection. He maintained a serum calcium concentration in the range of 6.4 mg/100 ml. The clinical course of this animal is depicted in Fig. 6d. When the parathyroid allograft was removed on day 60, the tissue was completely destroyed with no recognizable architecture remaining.

Discussion

Although it has been clearly demonstrated in several experimental animals[5,6,16] that parathyroid autografts can be successful in maintaining the host in normal calcium homeostasis, the experience with parathyroid allografts has been generally disappointing.

Almost 70 years ago, Halsted published his classical experiments on parathyroid transplantation in dogs.[7,8] He presented histologic evidence of autograft, but not allograft, survival; whether either of the grafts were successful in maintaining a normocalcemic state is unclear from his report.

Subsequent attempts to graft allogeneic parathyroid tissue by placing it into an immunologically privileged site such as the inside of a Millipore filter,[14] the anterior chamber of the eye,[4] or the brain[10] have all met with failure. Fisher and associates[4] recently attempted to allograft canine parathyroid glands into an immunosuppressed host. They found no evidence that allografted parathyroid tissue functioned; their attempts to autograft parathyroid tissue were also unsuccessful.

In contrast to these unsuccessful results, Russell and Gittes[11] have demonstrated that parathyroid glands could

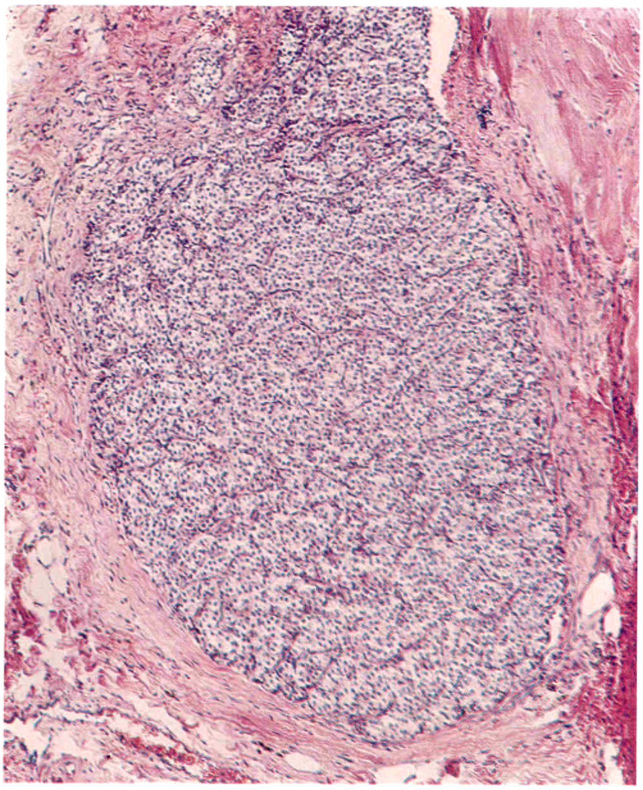

FIG. 5c

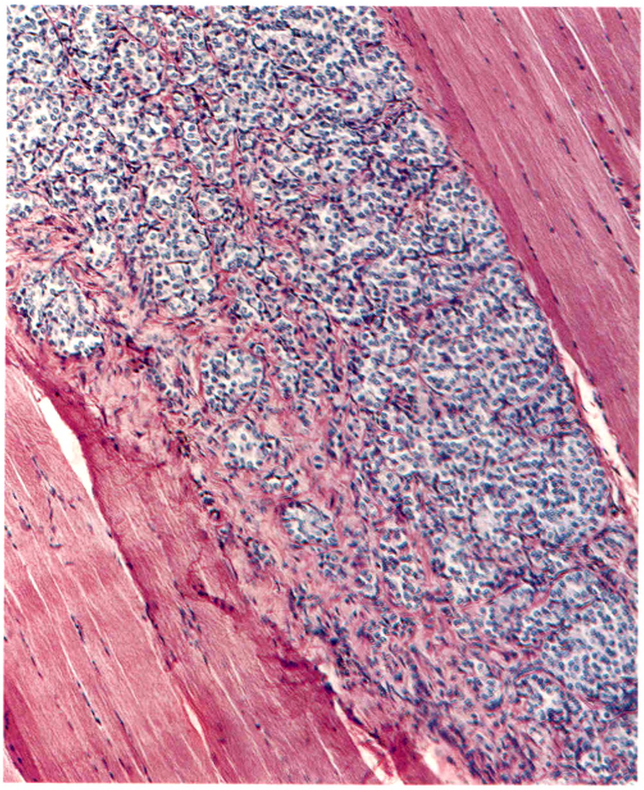

FIG. 5d

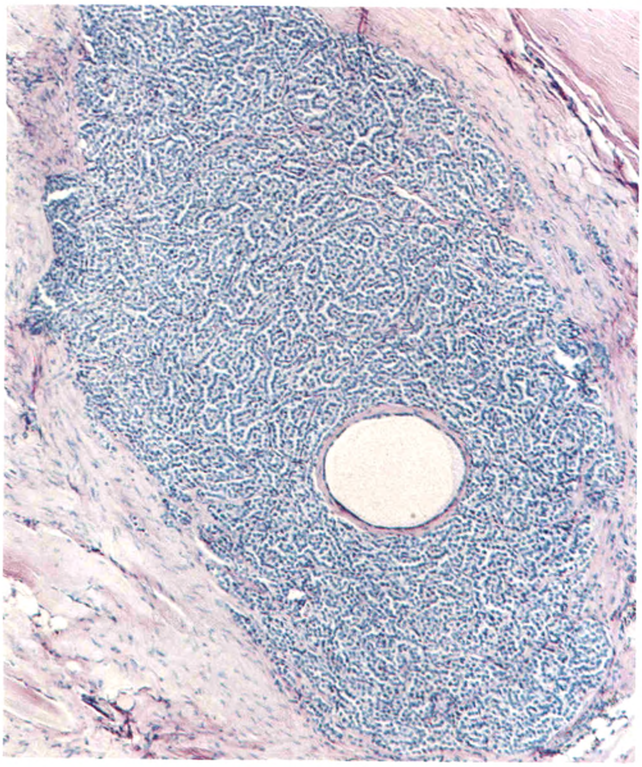

FIG. 5e

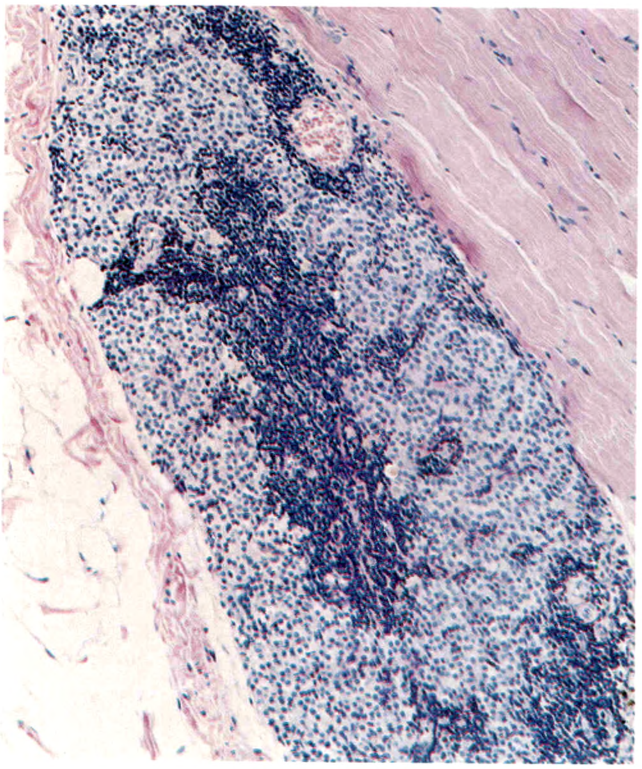

FIG. 5f

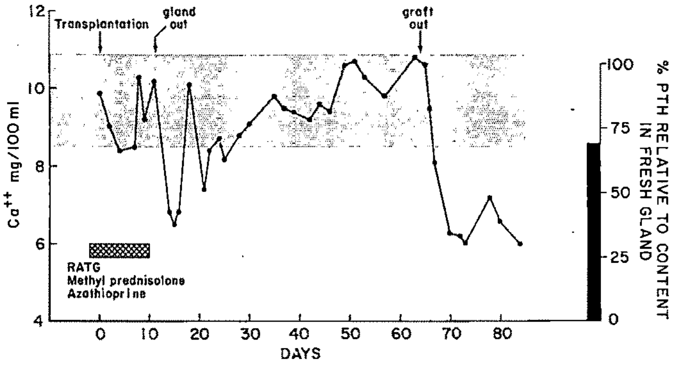

Fig. 6a. The time in days is shown on the abscissa. On the ordinate to the left is demarcated serum calcium concentration in mg/100 ml. On the ordinate to the right is represented parathyroid hormone content in the transplanted gland relative to PTH content in fresh parathyroid gland. Clinical course of dog B-26. Note drop and then gradual ascent of serum calcium concentration following removal of fourth parathyroid gland from the neck. A rapid fall in serum calcium occurs after parathyroid allograft removal on day 60. (RATG-Rabbit antithymocyte globulin.)

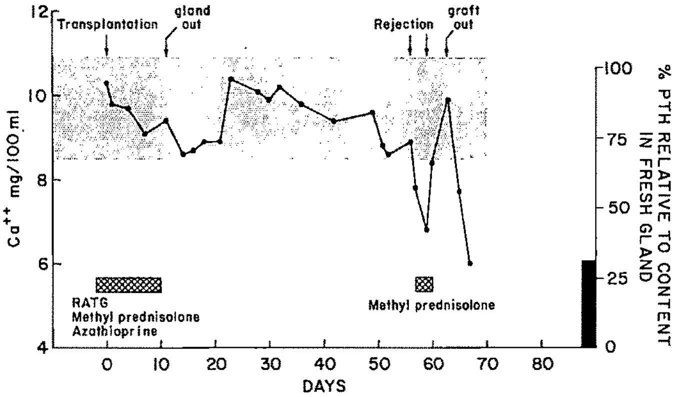

Fig. 6c. Clinical course of dog B-18. Note maintenance of serum calcium concentration within the normal range until immunological rejection on day 50. Treatment with methylprednisolone resulted in an increase in serum calcium concentration which fell again following removal of the parathyroid allograft on day 60.

be successfully allografted, without immunosuppression, between two strains of inbred rats. They attributed their success to the likelihood that parathyroid tissue had fewer histocompatibility antigens than skin, since skin allografts exchanged between the same two inbred strains were promptly rejected.

Our data clearly demonstrate that parathyroid glands, when minced into small pieces and transplanted intramuscularly as autografts, function sufficiently to maintain the host at a normal serum calcium concentration. That the animal is dependent on this transplanted parathyroid tissue alone can be demonstrated by removing the muscle bed containing the parathyroid graft and observing that the animal rapidly develops hypocalcemic tetany. Furthermore, histologic examination of the autografted tissue reveals normal parathyroid architecture, and radioimmunoassay of tissue extracts demonstrates high concentrations of parathyroid hormone. That the concentration of PTH in the grafted parathyroid gland and in fresh parathyroid tissue were not quantitatively the same is not surprising since the grafted parathyroid contains varying amounts of muscle and fibrous tissue around it.

Conversely, all seven of the non-immunosuppressed dogs who received parathyroid allografts showed no evidence of graft function. Each animal developed tetany within four to five days after its remaining autologous *in situ* parathyroid gland was removed. Histologically these allografts were characterized by a heavy mononuclear cell infiltration and occasional necrosis. Furthermore, radioimmunoassay measurement of the allografted pieces revealed extremely small concentrations of parathyroid hormone. We would conclude from this result that canine parathyroid tissue is indeed antigenic and that one would expect parathyroid allografts to be rejected in a manner similar to most other allogeneic tissues.

When the dogs were immunosuppressed prior to receiving a parathyroid allograft, however, the result was quite

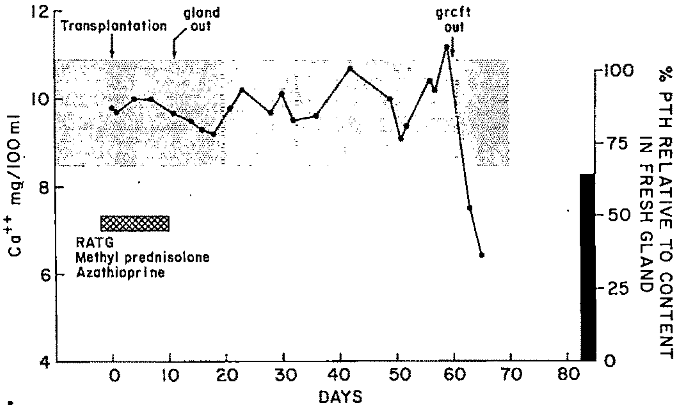

Fig. 6b. Clinical course of dog B-20. Note normal serum calcium concentration until day 60 when a rapid drop follows removal of the parathyroid allograft.

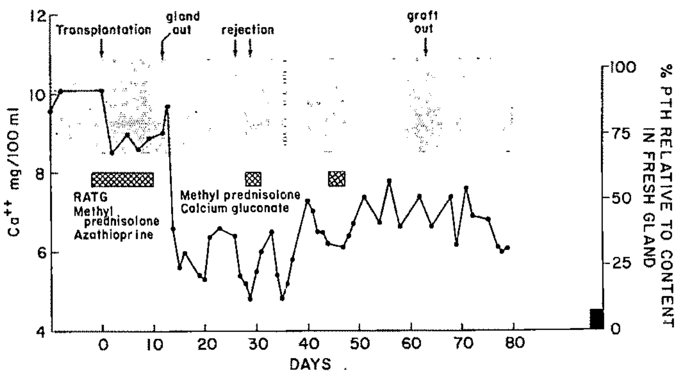

Fig. 6d. Clinical course of dog B-17. This animal never had any evidence of parathyroid graft function. The mean serum calcium concentration remained well below the normal range despite intermittent therapy with methylprednisolone and calcium gluconate.

different. Four of the six allografted beagles demonstrated no evidence of graft rejection throughout the course of the experiment. That the allograft was functioning could be readily demonstrated by removing the muscle bed containing the grafted parathyroid tissue. There was a prompt and progressive fall in the serum calcium concentration. Histological evaluation of the parathyroid allografts revealed normal parathyroid architecture with no evidence of immunologic rejection. Furthermore, appreciable quantities of PTH were detected in the grafts by radioimmunoassay. In one of the allografted immunosuppressed dogs, there was immunologic rejection which was successfully treated with intravenous methylprednisolone. In the sixth allografted immunosuppressed animal there was evidence of prompt and permanent immunologic rejection.

Several factors were probably responsible for our success in transplanting parathyroid glands. First, great care was taken to maintain sterile surgical technique. Second, the parathyroid pieces were cut into very small slivers prior to implantation. Immediately following grafting, the survival of parathyroid tissue depends on nutrition from surrounding tissue fluid. Obviously cells in the central portion of the tissue are at a disadvantage and undergo necrosis if the piece is too large. (Similar observations have also been made on parathyroid glands maintained in organ culture).[12] Third, by placing the removed parathyroid glands in cold tissue culture medium, they became firm and did not rupture or burst upon sectioning. Fourth, the implantation of the small parathyroid pieces well within a muscle bed is of foremost importance. We took care not to create hemorrhage at the site of implantation and were careful to close the fascia over each implanted piece. This prevented the transplanted parathyroid from extruding and also served as a marker for subsequent location. Some investigators[1] have advised placing a suture through the parathyroid tissue in order to hold it within the muscle bed. This frequently results in a foreign body reaction within the transplanted tissue and we have not used this method. Originally we also tried to implant parathyroid pieces within subcutaneous tissue or just below the muscle fascia, but neither of these sites proved as satisfactory as the intramuscular location. Fifth, the fact that our immunosuppressed dogs were beagle siblings from a partially inbred colony provided for a greater likelihood for success in transplantation than the use of random bred mongrels. Nevertheless, the grafts in two of the immunosuppressed dogs did undergo immunologic rejection. From previous experience we know that skin grafts do not survive when allografted between sibling pairs of this beagle colony. It was surprising that there was little relationship between graft rejection and DL-A identity. Dog B-17 totally rejected his DL-A identical allograft while in both dogs with a two haplotype difference (B-26) and B-27) there was no evidence of allograft rejection.

Our data indicate that parathyroid allografts function only if the host is immunosuppressed. Graft viability and function can be readily evaluated by histologic, biochemical and radioimmunoassay methods.

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Treatment of the Severely Burned Child With Skin Transplantation Modified by Immunosuppressive Therapy

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The IgG fraction of equine antithymocyte globulin administered by the intravenous and intramuscular route to two patients with severe thermal injury was associated with survival of the skin allografts to 19 and 42 days. In the second patient the IgG fraction was discontinued 28 days after skin grafting and rejection occurred 14 days later while the patient was receiving azathioprine and 1% topical hydrocortisone cream to the skin allografts. Although no comparison can be made between the immunosuppressive properties of antithymocyte globulin, azathioprine and topical steroids, skin allograft survival was prolonged temporarily until autograft skin from previous donor sites could be obtained. The use of skin allografts protected by immunosuppressive therapy in patients with severe thermal injury deserves further consideration.

SKIN AUTOTRANSPLANTATION is the accepted method of treatment for patients with large areas of full thickness skin loss secondary to thermal injury. However, there are circumstances where the surface area of the burn is so great that the remaining viable skin is insufficient for autograft coverage. The use of skin heterografts applied at frequent intervals provides temporary coverage and avoids prolonged loss of protein and fluid. In severely burned patients, this procedure may be necessary for weeks until previous donor sites can be reused for autografting. The sporadic use of skin allografts in the past for coverage of full thickness burn sites has failed because of early graft rejection. In some instances survival was extended beyond the usual 10–14 days without immunosuppressive drugs. This prolongation may be in part related to the effects of severe thermal injury upon the immune response causing decreased levels of serum complement and IgG[1] as well as impairment of the patient's ability to respond to delayed hypersensitivity.[8] Ceppellini[4] observed that skin allografts compatible in the ABO blood system have a longer survival than those with ABO incompatible donor recipient combinations. Chambler[5] and Batchelor[2] noted human skin allograft survival to be related to HLA histocompatibility between the donor and recipient. These observations suggested that human skin allograft survival might be prolonged even further if ABO compatible skin from related donors is transplanted to recipients receiving immunosuppressive therapy. Permanent or even prolonged temporary skin coverage of large areas of third degree burn would be of significant value in the treatment of severely burned patients without available donor sites.

This paper reports two patients with more than 75% third degree flame burns treated by the application of related donor skin allografts using equine anti-human thymocyte globulin alone and combined with azathioprine and hydrocortisone cream as immunosuppressive therapy.

Materials and Methods

Preparation of Antithymocyte Globulin

Human thymus tissue, sliced into fine pieces 1–2 mm thick, was gently compressed together by a fine silk filter. The filter retained the thymic stroma allowing passage of the thymocytes into the buffered saline. Cell viability was 85–90% as determined by *Trypan* blue. The horse was first immunized by an intramuscular injection of equal volumes of thymocytes (1–3 × 10^9 cells) and complete Freund's adjuvant. Twenty-one and 28 days later the horse received an intravenous injection of saline thymocyte suspension with a similar cell count. The horse was then bled 7 days after the second intravenous injection. One month later the horse received another intravenous injection of a similar concentration of thymocytes and was bled

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for the second and final time in 1 week. All horses immunized according to this schedule were bled only twice. The serum was separated and decomplemented. The hemagglutinin antibody, removed by two absorptions with human red cell stroma, was reduced to a titer of less than 1 : 32. The IgG fraction of the ATG was then prepared by the batch technique using DEAE sephadex.[7] The lymphagglutinin titer of the IgG material ranged from 1 : 729 to 1 : 19,000. The purity of this preparation was confirmed by immunoelectrophoresis. The material was stored in 50 cc aliquots in plastic bags, frozen and sterilized by high energy irradiation.

Primate Skin Graft Test System

Four Rhesus monkeys were selected at random and skin grafted. The monkeys were treated intravenously with the IgG fraction of the equine ATG prepared against the human thymocyte (50 mg/kg/day). The immunosuppressive schedule included administration of the IgG 1 day pretransplantation and again on the 3rd and 5th post-transplant days. The skin grafts (6 in number) were applied to the lateral chest wall and protected by a thoracic plaster cast. The cast was divided for graft inspection every 3 days from the 7th to the 21st post-transplant day. During each inspection the grafts were also palpated, and biopsy specimens obtained on day 14 and 21. At 21 days approximately 20% of each of the six grafts were soft, pink and appeared viable; the remaining portion of the graft was hard and firm with retraction and elevation from the host skin. A biopsy of the graft at this time revealed considerable infiltration with mononuclear cells and separation from the underlying granulation tissue. The end point of skin graft survival was considered to be 21 days. Four other monkeys were treated by the subcutaneous injection of the IgG fraction of ATG (2–4 mg/kg/day) 7 days before skin grafting and 14 days afterwards. Skin allografts in this instance were prolonged to 21 days using the same criteria.

Tissue Typing

Histocompatibility matching, performed by a modification of the cytotoxicity technique of Terasaki, was completed prospectively in one of the two recipient patients. Lymphocytotoxicity crossmatch using recipient serum and donor lymphocytes was performed.

Case Reports

Case No. 1 C.H., #E19-03-39: A six-year-old, black girl (18 kg) was admitted to the University Hospital with 75% third degree flame burn of the body surface. The patient was resusitated with intravenous fluids, blood and antibiotics. Partial excision of the eschar was performed 1 week later covering the open wounds with porcine skin heterografts. The patient was considered for skin transplantation because of the paucity of donor autograft sites. The recipient and her donor father were ABO compatible; however, tissue typing was unsuccessful. Skin allografts from the anterior surface of both thighs of the donor were applied to the anterior abdominal wall and anterior thighs of the recipient 15 days post-burn injury. The only immunosuppressive treatment administered was the intravenous IgG fraction of equine ATG during a 4 hour period (70 mg/kg/day in 500 cc of isotonic saline, pH 7.4). This was given 1 day before transplantation and day 3, 8, 12 and 13 after skin transplantation. The hospital course was complicated by fever, inanition and septicemia with pseudomonas and aspergillus. Gangrene of the right upper extremity developed requiring a forearm amputation 16 days after transplantation. Although it appeared that infection, primarily pseudomonas, caused the loss of most of the grafts, it was difficult to exclude rejection as a contributing factor. Approximately 15% of the skin allografts not affected by infection remained soft, pliable and adherent to the underlying granulation tissue until death, 19 days post skin transplantation. Porcine skin heterografts applied at the same time as the allografts were rejected 6–8 days later. An autopsy was not obtained.

Case No. 2 J.A., #E22-44-49: A five-year-old white, boy (20 kg) was admitted to the University Hospital with a 75% flame burn involving the chest, back, abdomen, upper extremities and both thighs circumferentially (Fig. 1). Resuscitation in the immediate post-burn period was achieved with intravenous fluids, antibiotics and whole blood. During the next 5 weeks, large areas of third degree burn tissue were excised from the chest, back, abdomen, and extremities, covering this area temporarily with procine skin heterografts. Autografts were then applied to the wrists, hands, axilla, perineum and suprapubic area until all available donor sites were exhausted. The mother and child were both ABO compatible (A positive) and on tissue typing found to have one mismatch (HLA-11) in testing for 13 antigens. The patient was treated with the IgG fraction of equine antithymocyte globulin (70 mg/kg/day) 4 days and 2 days preoperatively, administered intravenously in 500 cc of isotonic saline pH 7.4 during a 5 hour period. Skin allografts obtained from the mother's thigh were applied primarily to the back and thigh of the recipient (Fig. 2). Porcine skin heterografts and a small area of autograft skin were applied simultaneously to the back. Postoperatively, the patient received the IgG

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Fig. 1. (Overleaf) The third degree burn area of the back of a 5-year-old child (Case No. 2) 10 days post-burn injury showed early separation of the eschar.

Fig. 2. Application of skin allografts from the mother to the recipient's back 39 days after burn injury.

Fig. 3. Biopsy of autograft skin 16 days after surgery with complete acceptance. The microscopic section appears unremarkable except for the usual process of healing with occasional polymorphs.

Fig. 4. Biopsy of allograft skin 16 days post-transplantation. Infiltration of mononuclear cells and polymorphs were present within the granulation tissue of the graft. This cell population was scattered throughout the sections of tissue examined even though the skin appeared grossly normal.

Fig. 5. Skin allografts were completely accepted 34 days after transplantation. The skin was soft, pliable and appeared indistinguishable from the autografts applied at the same time.

Fig. 6. Microscopic section from the rejecting skin allografts 6 weeks post-transplantation. The dermis had separated from the host granulation tissue with a marked inflammatory response characterized by lymphocytes, plasma cells and polymorphs. To the naked eye the skin was erythematous, indurated with desquamation of the epithelium.

Fig. 7. The area of previous skin allografts, now completely rejected, is adequate for autotransplantation. The entire process of rejection took place in 10 days without evidence of a systemic response to the foreign antigen.

Fig. 8. The previous burn area, originally covered with allografts, was completely healed with skin autografts taken from previous donor sites.

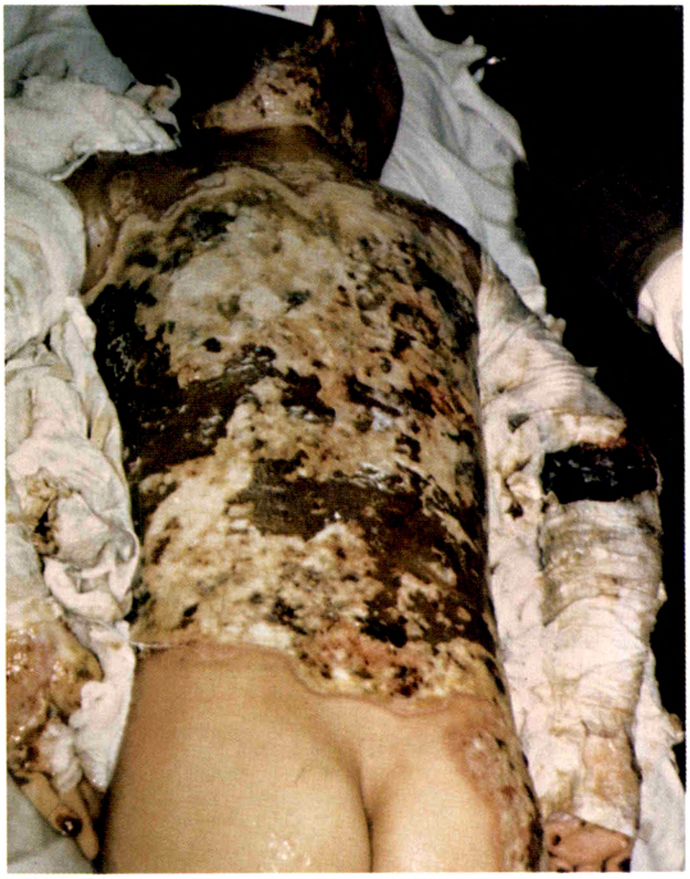

FIG. 1.

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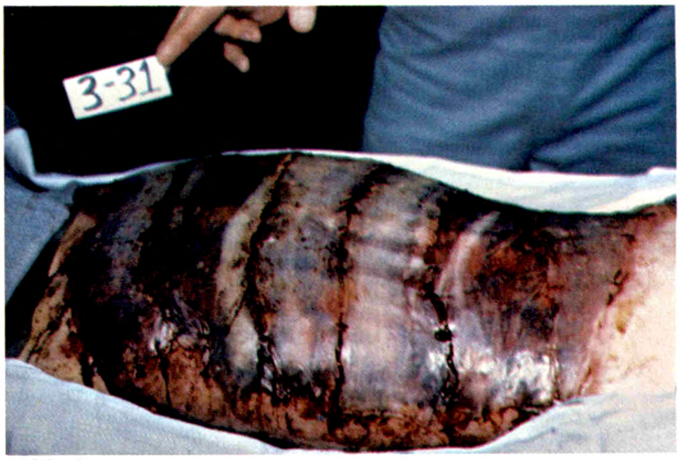

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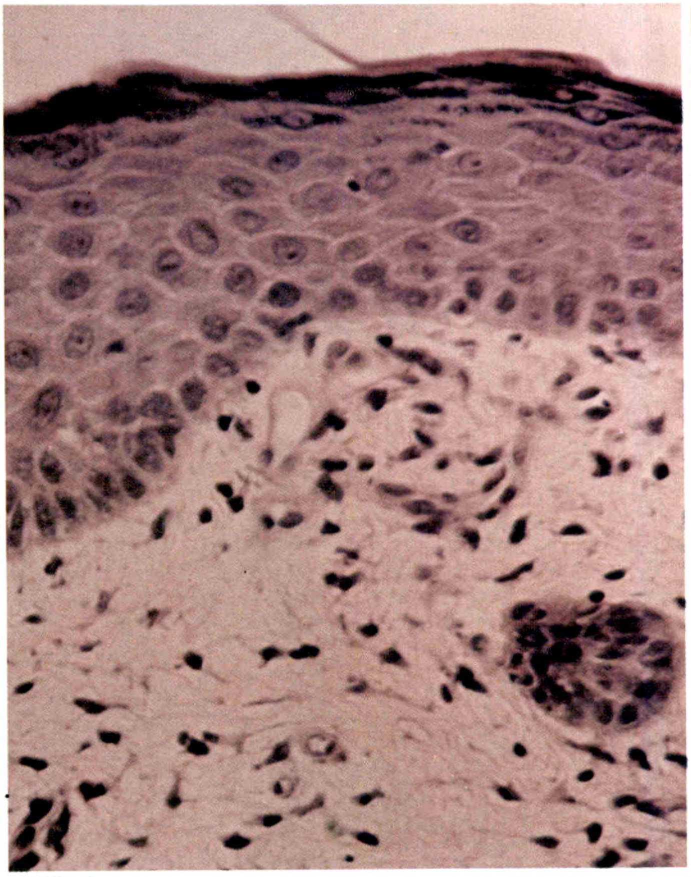

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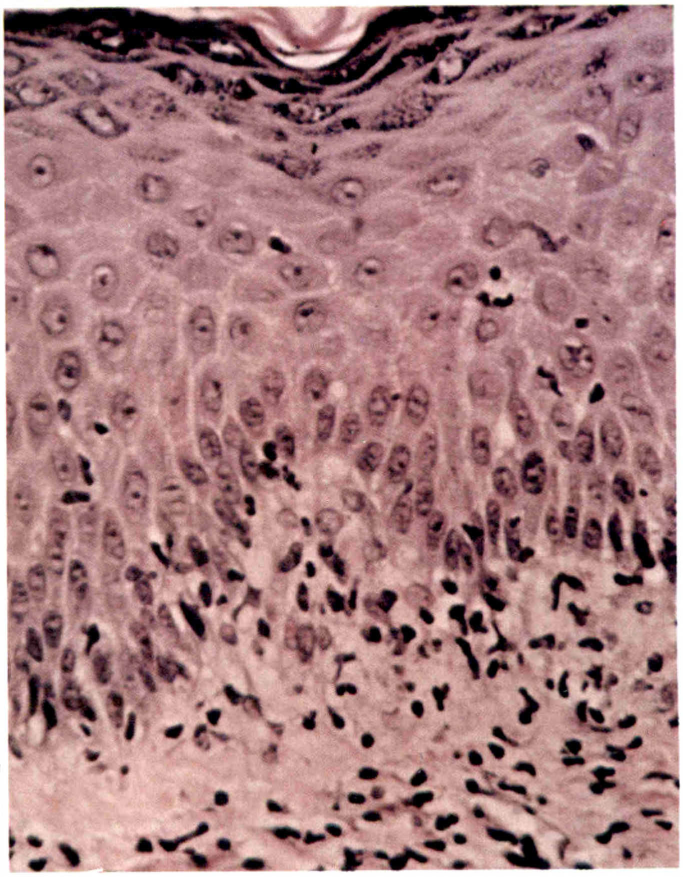

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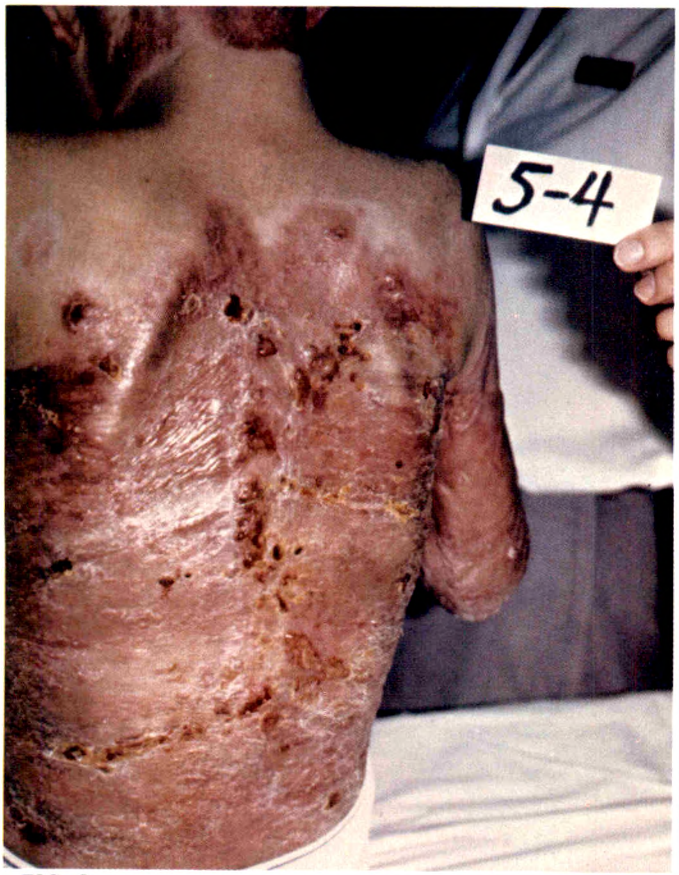

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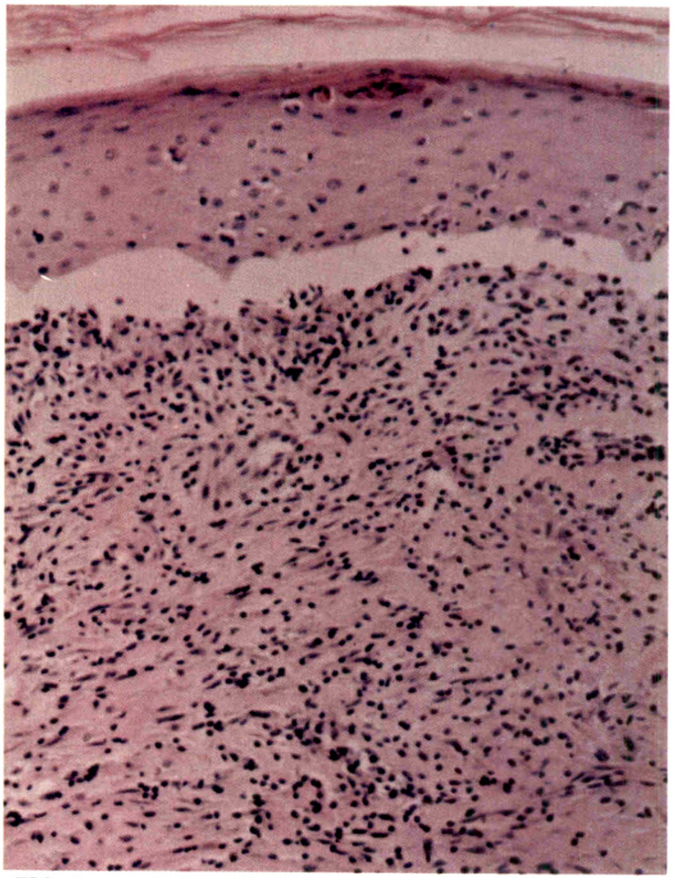

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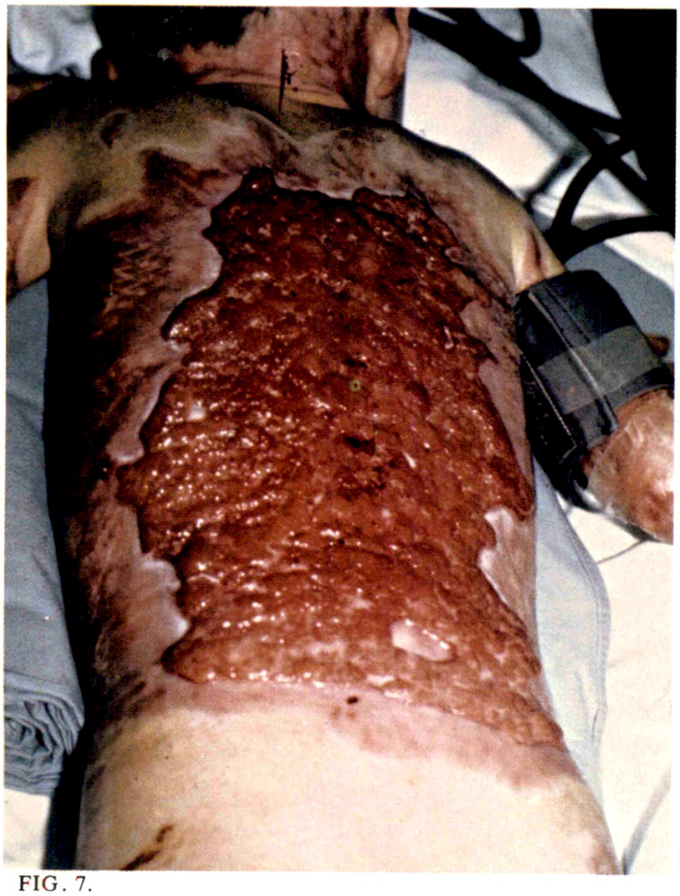

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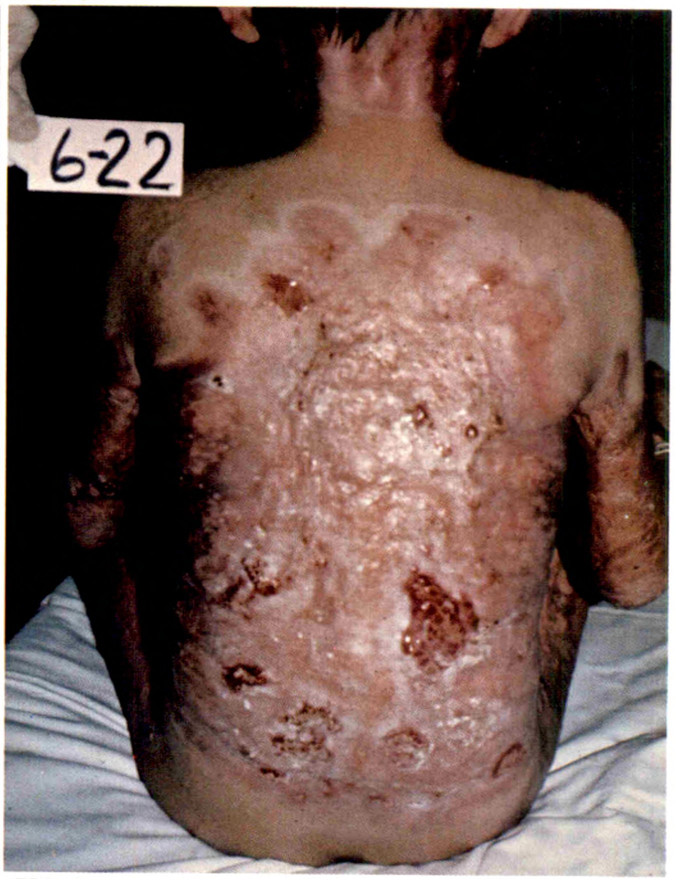

FIG. 8.

fraction of equine ATG on days 1, 6, 7 and 8 (50 mg/kg/day). Fever and leukocytosis were present during this time and appeared to be related in part to the intravenous administration of the IgG. From the 10th to the 25th postoperative day the IgG was given daily by the intramuscular route (4 mg/kg/day). The skin allografts were accepted with a 90% take and appeared indistinguishable by both palpation and their gross appearance from the skin autografts. Biopsies of the autograft and allograft skin were obtained 3 weeks post-transplantation, (Figs. 3 and 4). During this time the child was completely ambulatory, free of dressings, gained weight and became afebrile. He was discharged from the hospital 1 month after transplantation (Fig. 5). Because the patient lived a considerable distance from the hospital which precluded his receiving daily injections of IgG, he was placed on azathioprine 25 mg/day and hydrocortisone cream (1%) applied topically each day to the transplanted skin. The patient was seen twice weekly as an outpatient for the next 2 weeks during which time the allografted skin remained unchanged. Six weeks post-transplantation the skin grafts were noted to be erythematous and indurated with areas of desquamation. A skin biopsy at this time revealed microscopic signs of rejection (Fig. 6), and the azathioprine was discontinued when the diagnosis of rejection was confirmed. During the next 7 days, all of the skin allografts were rejected (Fig. 7). The patient's general condition remained excellent, and previous donor sites now healed were reused applying autograft skin to the previous area of skin transplantation. The autografts were completely accepted, and the patient discharged 6 months after his original burn injury (Fig. 8).

Discussion

This application of skin allografts in severely burned patients, modified by the administration of antithymocyte globulin, azathioprine and hydrocortisone cream was an attempt to cover large areas of granulating wounds in individuals without available donor sites for autografts. This form of treatment obviated the need of frequent dressing changes required in the use of heterografts and if successful, at least temporarily would permit a rapid recovery as noted in Patient No. 2. The effect of the immunosuppressive therapy used in these two patients cannot be determined with certainty since the burn injury itself may have altered the immune response of the patient. The effectiveness of ATG and azathioprine combined as immunosuppression was even more difficult to assess when one considered the data of Batchelor[2] indicating survival of skin grafts in well-matched patients as determined by histocompatibility testing to exceed that of grafts in poorly matched individuals. Burke *et al.*[3] reported the use of skin allografts from related donors in three severely burned children treated only with azathioprine. The transplanted skin was used as temporary skin coverage in each instance until previously used donor sites became available. The use of azathioprine in their patients did not seem to increase the incidence of infection. Bacterial flora of the burn wound was similar to the non-immunosuppressed patient, and episodes of bacteremia responded to antimicrobial therapy.

The two patients presented in this paper represented an attempt to provide skin coverage in individuals with severe thermal injury and large areas of third degree burn. In both instances donor sites had been exhausted, and it was hoped that prolonged temporary skin coverage would alter the catabolic state. The first patient, C. H., was grafted 15 days post-burn injury soon after excision of the eschar. Bacterial contamination was already present in the subcutaneous tissues and probably contributed to the subsequent graft infection. Eighty-five per cent of the allografts became infected and sloughed although those areas of transplanted skin not infected remained viable until death of the patient 19 days after transplantation. The second patient, J.A., was managed with autografts to the axilla, hands, arms and perineum until all donor sites were used. At this time, 9 weeks post-burn injury, the recipient's burn areas were clean, granulating, and ready for allografting. The complete acceptance of the transplanted skin in this patient for 6 weeks was most encouraging. The substitution of azathioprine and 1% topical hydrocortisone cream for ATG was necessary because of the inability to continue daily injections after discharge from the hospital. This manuever obscured the answer to the question of the effectiveness of ATG as the sole immunosuppressive agent for a prolonged period of time. However, even a temporary period of skin coverage was extremely valuable in the management of this patient. It was of interest that the porcine heterografts applied to both patients were rejected completely between 7 and 10 days. During the rejection episode in Patient No. 2 the transplanted skin became erythematous and edematous with complete desquamation during a 7–10 day period. There was no evidence of a generalized systemic response to the rejecting allografts as noted by Holman,[6] and although a low grade fever persisted during the time of rejection, no other systemic complaints were observed.

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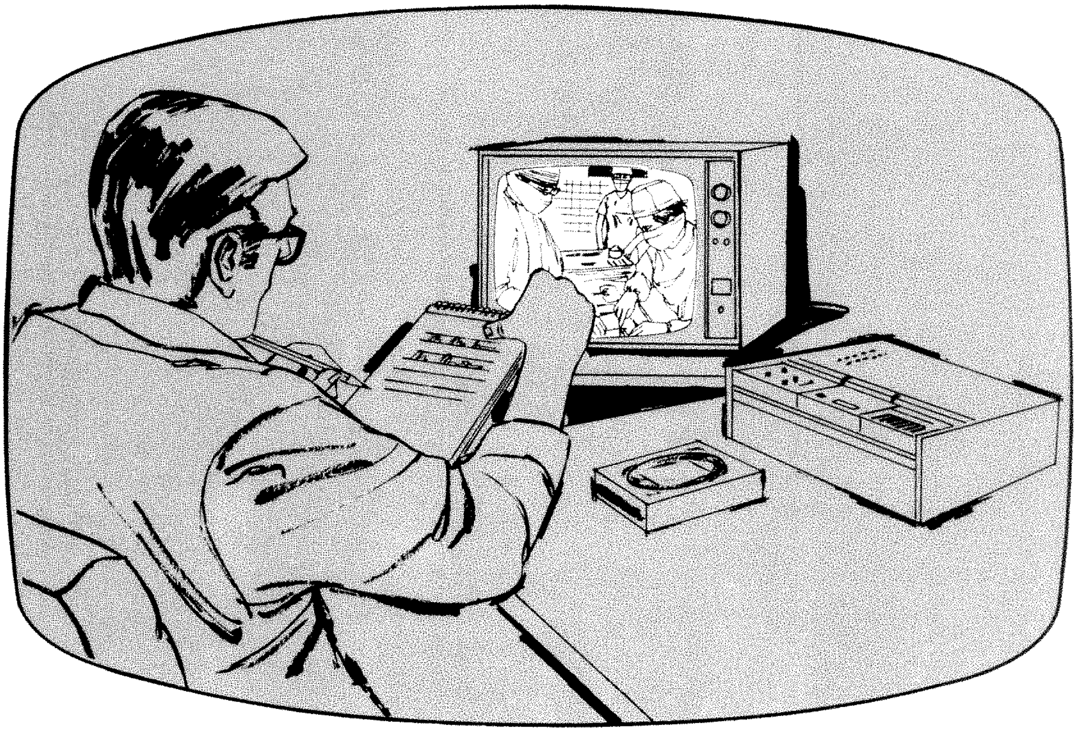

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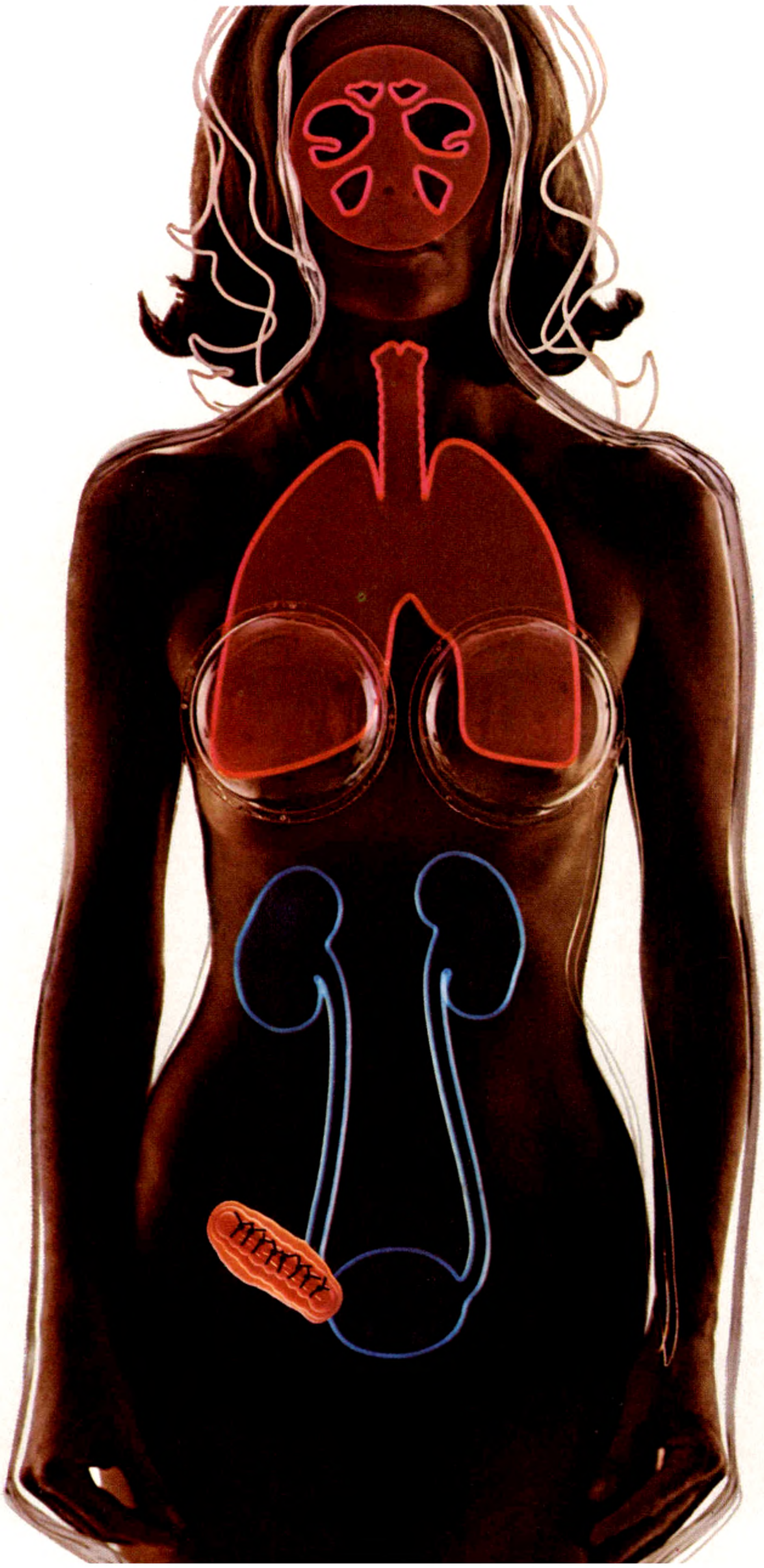

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A New Oral Antibiotic with these Important Features:

- **Bactericidal activity *in vitro.***
- **Effective against a wide range of Gram-positive and Gram-negative infections due to susceptible organisms:**

Respiratory tract infections caused by group A beta-hemolytic streptococci and *D. pneumoniae.*

Urinary tract infections caused by *E. coli, Pr. mirabilis,* and *Klebsiella* species.

Skin and soft-tissue infections caused by staphylococci.

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae, H. influenzae* and staphylococci.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

- **Documented safety.**
- **Rapidly absorbed. Average peak serum levels within 1 hour.**

(Approximately 9 and 16.5 mcg./ml. at 1 hour with 250 and 500 mg. capsules, respectively, in normal adult volunteers.)

- **High urinary levels.**

(Peak concentration of approximately 3200 mcg./ml. with 500 mg. capsule dose in normal adult volunteers.)

- **Excreted essentially unchanged in the urine.**
- **Acid stable. Can be given without regard to meals.**

'Anspor' is contraindicated in patients with known hypersensitivity to the cephalosporins. **In penicillin-sensitive patients, cephalosporin C derivatives should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.**

Adverse Reactions

The following adverse reactions have been reported: glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn; mild urticaria or skin rash, pruritus, joint pains; transient eosinophilia, leukopenia, neutropenia; transient rise of SGOT, SGPT, total bilirubin, BUN; dizziness, tightness in the chest, and candidal vaginitis.

For a brief summary of prescribing information, including indications, contraindications, warnings, precautions, adverse reactions, and dosage, please see the following page.

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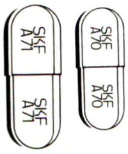

capsules: 250 and 500 mg.
for oral suspension: 125 and 250 mg./5 ml.

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

DESCRIPTION
Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid.

ACTIONS
Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephradine is active against the following organisms *in vitro*:

Beta-hemolytic streptococci	*Diplococcus pneumoniae*
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains	*Escherichia coli*
	Proteus mirabilis
	Klebsiella sp.
	Hemophilus influenzae

Note—Some strains of enterococci *(Streptococcus faecalis)* are resistant to cephradine. It is not active against most strains of *Enterobacter* sp., *Pr. morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephradine and methicillin-type antibiotics.

INDICATIONS
Anspor (cephradine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated microorganisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae*.

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*, *Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS
Anspor (cephradine, SK&F) is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS
IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephradine is secreted in breast milk during lactation.

PRECAUTIONS
Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy as cephradine accumulates in the serum and tissues. See *DOSAGE AND ADMINISTRATION* section for information on treatment of patients with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephradine therapy, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS
The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pruritus, and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the chest and candidal vaginitis.

DOSAGE AND ADMINISTRATION
Anspor (cephradine, SK&F) may be given without regard to meals.

Adults: For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally spaced doses. For acute infections of the urinary tract, including prostatitis, and pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equally divided and spaced doses. For otitis media due to *H. influenzae*, doses from 75 to 100 mg./kg./day in equally divided and spaced doses are recommended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram, q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule is necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance dose is 500 mg. at following time intervals: creatinine clearance >20 ml./min., 6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-24 hours between doses; creatinine clearance 10-14 ml./min., 24-40 hours between doses; creatinine clearance 5-9 ml./min., 40-50 hours between doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

HOW SUPPLIED
ANSPOR (cephradine, SK&F) Capsules—250 and 500 mg.

'ANSPOR' for Oral Suspension—Pleasant fruit-flavored oral suspension which, after reconstitution, provides 125 mg. or 250 mg. of cephradine per 5 ml. teaspoonful.

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A New Oral Antibiotic

Nonocclusive Mesenteric Vascular Insufficiency

FAWZI HABBOUSHE, M.D.,* HERBERT W. WALLACE, M.D., MOREYE NUSBAUM, M.D.,
STANLEY BAUM, M.D.,† PAUL DRATCH, M.D.,‡ WILLIAM S. BLAKEMORE, M.D.§

A case of nonocclusive mesenteric vascular insufficiency in a patient with congestive heart failure on digitalis and with arrhythmia is presented. The preoperative diagnosis was made through mesenteric arteriography. A course of treatment was followed which we believe prevented intestinal gangrene. This regimen includes measures to increase cardiac output, local pharmacologic agents to induce mesenteric vasodilatation, antibiotics, and oxygen. The viability of the intra-abdominal organs was demonstrated by laparotomy.

THE ENTITY of nonocclusive mesenteric vascular insufficiency has enjoyed increasing recognition. Twenty per cent to 36% of reported cases of acute mesenteric vascular insufficiency have been of the nonocclusive type.[2,6,14] This condition, which occurs most often in elderly individuals with heart disease, is associated with low cardiac output syndromes, such as congestive heart failure[2] and arrhythmia, and with digitalis administration,[11,12,17] all associated with a diminution in splanchnic blood flow. This may be severe enough to cause bowel ischemia without demonstrable obstruction of major mesenteric vessels. The mortality rate of patients with nonocclusive vascular insufficiency has been alarmingly high, 80–100%.[6,14,15] In the case presented in this report the condition was diagnosed preoperatively by superior mesenteric arteriography and was managed conservatively with vasodilating agents infused in the mesenteric arterial system with a successful outcome. The use of this diagnostic technique might lead to a reduction in the mortality rate associated with nonocclusive mesenteric vascular insufficiency.

From the Departments of Surgery and Radiology, School of Medicine, and the Graduate Hospital, University of Pennsylvania, Philadelphia, Pennsylvania

Case Report

L.J., a 49-year-old Negro female, was first admitted to the Graduate Hospital of the University of Pennsylvania in November 1967, at which time she underwent an open commissurotomy for mitral stenosis with atrial fibrillation. Cardioversion restored normal sinus rhythm postoperatively, and she was subsequently maintained with quinidine, 200 mg q.i.d., and digitoxin, 0.1 mg daily. She apparently remained asymptomatic until August 1970, when she came to the Accident Ward complaining of continuous sharp epigastric pain of 24 hours' duration. This had been preceded by intermittent mild epigastric pain beginning one week prior to admission. She denied vomiting, diarrhea, and fever. She had been constipated for one week and had passed only small amounts of flatus the day before.

On physical examination the patient was afebrile. She was pale and sweaty in the head and neck region. The apical pulse was 52 per minute with bigeminal rhythm, and her blood pressure was 120/70. There was a systolic murmur, grade III/VI, at the left fourth interspace, heard maximally at the left sternal border. She had definite ankle edema. The chest contained a few scattered rales at the bases of the lungs. The abdomen was soft with slight tenderness in the epigastrium but no rebound tenderness. There was a vague, pulsating mass in the epigastrium and extending across the right upper quadrant. The enlarged liver was felt 4 cm below the costal margin. The hepatojugular reflex was absent, and the liver edge was not sharp. With the presence of a pulsatile mass, the possibility of a leaking abdominal aortic aneurysm was considered.

Laboratory data included: serum amylase 60 units; blood urea nitrogen 7 mg%; hemoglobin 13.4 gm%; hematocrit 40%; white blood count 10,800/cmm with a normal differential; serum sodium 143 mEq/L, potassium 3.6 mEq/L, chloride 97 mEq/L, CO_2 content 35 mm/L; blood sugar 95 mg%.

A flat plate of the abdomen revealed a thick-walled, dilated loop of bowel in the left lower quadrant. A midstream aortogram showed a normal aortic lumen without evidence of an aneurysm. The superior mesenteric arteriogram revealed a marked narrowing of the medium and small arteries during the arterial phase and a markedly reduced flow with faint visualization during the venous phase.

Thirty hours after admission the patient complained of generalized abdominal pain. Although she was still afebrile, she had a soft, distended abdomen, mild tenderness in the lower quadrant without rebound tenderness, and markedly diminished bowel sounds. A repeat transfemoral superior mesenteric arteriogram showed the same findings as

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Reprint requests: Dr. Herbert W. Wallace, Department of Surgery, Graduate Hospital of the University of Pennsylvania, 19th and Lombard Streets, Philadelphia, Pennsylvania 19146.

the previous one (Fig. 1a), suggesting nonocclusive superior mesenteric ischemia of the small bowel. Injection of 25 mg tolazoline hydrochloride via an indwelling selective superior mesenteric arterial catheter led to a marked improvement in the splanchnic circulation, as shown on subsequent arteriograms (Fig. 1b). An epidural catheter was inserted at level T7-T8, and 8 cc of 1% xylocaine was injected via this catheter every four hours. These injections, alternating with an injection of tolazoline hydrochloride, 25 mg every four hours, provided almost continuous splanchnic vasodilatation. The patient was placed on oral neomycin, 1 gm every six hours. The patient's abdominal symptoms abated within ten hours.

During the next 40 hours the white blood count rose progressively to 20,000/cmm with a shift to the left. Although the patient's abdomen was soft, there was rebound tenderness in the left lower quadrant. A superior mesenteric arteriogram again showed marked slowing of the mesenteric circulation. This was thought to be related to the fact that the last dose of vasodilator had been administered more than two hours previously. After an epidural injection a repeat arteriogram showed a marked increase in the splanchnic flow (Fig. 2). The persistent abdominal findings despite adequate splanchnic vasodilatation in response to drugs prompted us to explore the patient surgically with the provisional diagnosis of gangrenous bowel.

The peritoneal cavity contained a small amount of serous fluid. The liver appeared normal. Within the first three feet of the upper jejunum were two slightly edematous segments with shaggy serosa but normal color. Peristaltic activity was sluggish. The remainder of the bowel was essentially normal. The major arteries, as well as the arcades and the jejunal branches, displayed good pulsations, and the veins appeared patent. There were no enlarged lymph nodes. Injection of 10 mg of tolazoline hydrochloride via the superior mesenteric catheter was followed by increased pulsations in the mesenteric arcades but no change in the color of the involved bowel segments. Since the bowel appeared to be viable, the abdomen was closed and the procedure was terminated.

The patient was managed postoperatively with oxygen, nasogastric suction, cautious administration of fluids, antibiotics, and discontinuance of digitoxin. Pharmacologic mesenteric dilatation was reinstituted for an additional 48 hours. Her postoperative course was complicated only by ileus of three days' duration and by a superficial infection of the wound. She was discharged in satisfactory condition on the seventeenth postoperative day. A mesenteric arteriogram performed immediately before discharge revealed an essentially normal mesenteric circulation (Fig. 3b).

Discussion

This case represents the constellation of clinical and laboratory findings reported to be associated with nonocclusive mesenteric insufficiency. The presence of congestive heart failure, digitalis intake, and arrhythmias, as well as a high hematocrit, contributes to diminished mesenteric flow, particularly at the microcirculation level. The incidence of congestive heart failure with this disease has been reported to be 80–90%.[2,14] While this reduces cardiac output, the association of arrhythmias, as in our case, further diminishes blood flow. This has been borne out experimentally by Corday *et al.*[8] Digitalis intake can further augment the deleterious effect on intestinal viability.[3,10] Both mesenteric vasoconstriction and hemorrhagic enteropathy have been ascribed to digitalis.[3] Fogarty and Fletcher[11] described a triad associated with nonocclusive mesenteric vascular insufficiency consisting of congestive heart failure, digitalis intoxication, and a marked elevation of hematocrit. Furthermore, these findings have been reported in other states associated with a low cardiac output, such as hemorrhagic shock, with resultant gangrene of the intestine.[15] Bounos[4,5] reports success in preventing this hemorrhagic enteritis by changing the intestinal milieu. While splanchnic vasoconstriction is a useful compensatory mechanism, it is apparent that a detrimental reduction in

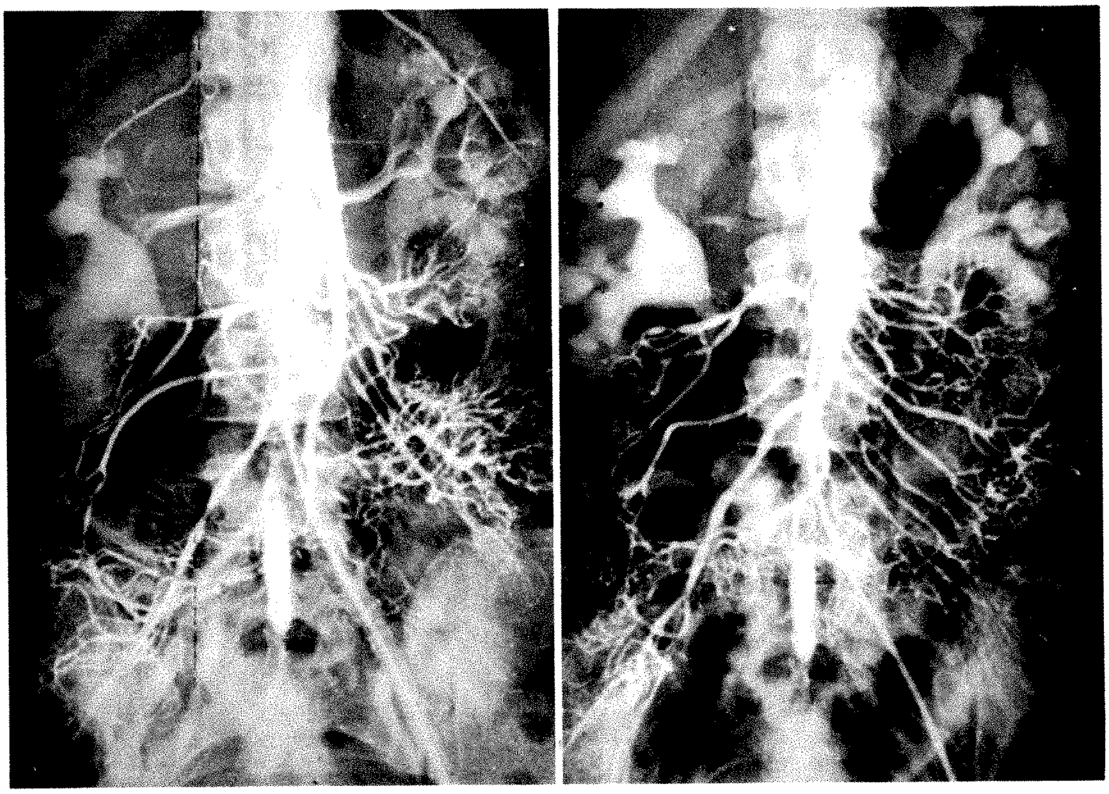

FIG. 1a (Left). Selective superior mesenteric arteriogram demonstrating multiple segmental areas of narrowing of both small and medium-sized vessels. There is a marked decrease in the peripheral perfusion of the smaller mesenteric branches and reflux of dye into the aorta. FIG. 1b. (Right) Selective superior mesenteric arteriogram after the injection of 25 mg of tolazoline hydrochloride, demonstrating dilatation of many of the segmental areas as well as an increase in peripheral arterial filling.

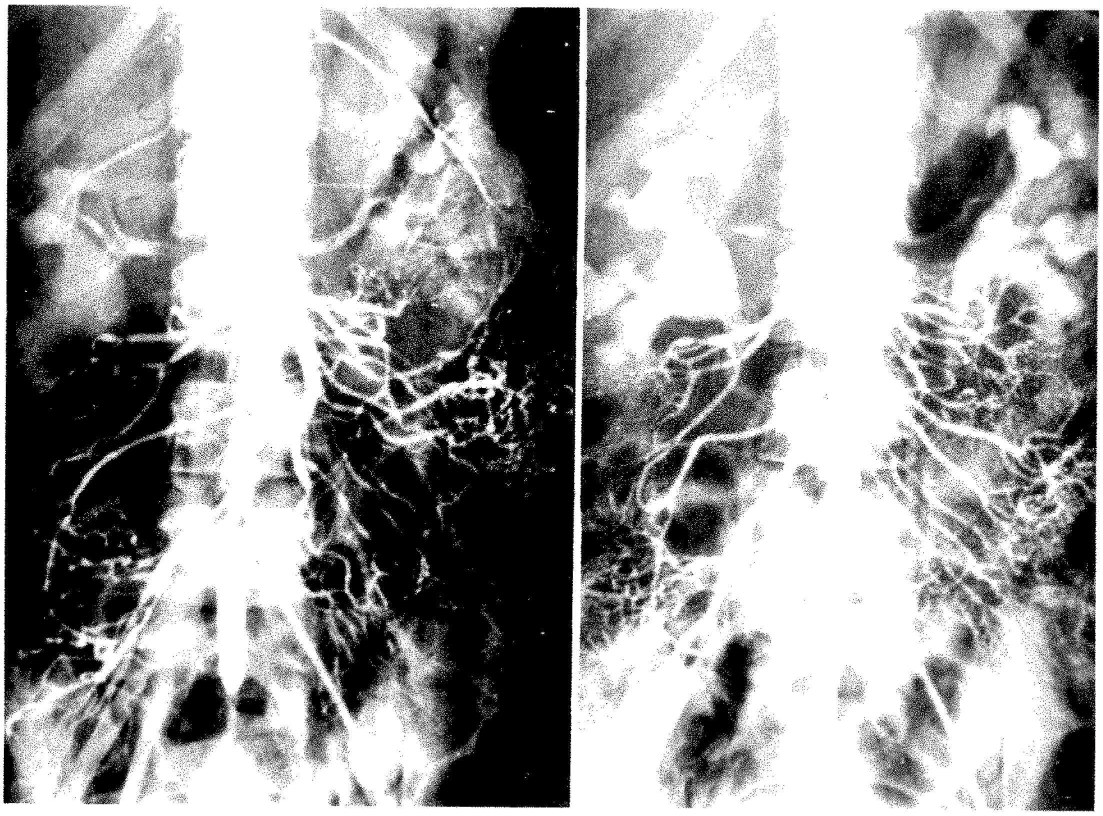

FIG. 2a (Left). Arteriogram done just before the injection of xylocaine into an epidural catheter, again demonstrating segmental narrowing and marked diminution of peripheral perfusion. FIG. 2b (Right). Arteriogram done after epidural block, revealing change of the above findings to a more normal pattern of perfusion.

flow can occur, particularly when augmented vascular reactivity is enhanced by associated factors such as hemoconcentration and digitalis.

A high index of suspicion is the prerequisite to accurate diagnosis and treatment of mesenteric vascular disease. In states in which the splanchnic circulation is thought to be diminished, unexplained abdominal signs and symptoms should be viewed with the possibility of mesenteric vascular insufficiency and intestinal necrosis in mind. Angiography stands as the single most important diagnostic aid in establishing the diagnosis once a high degree of suspicion is aroused.

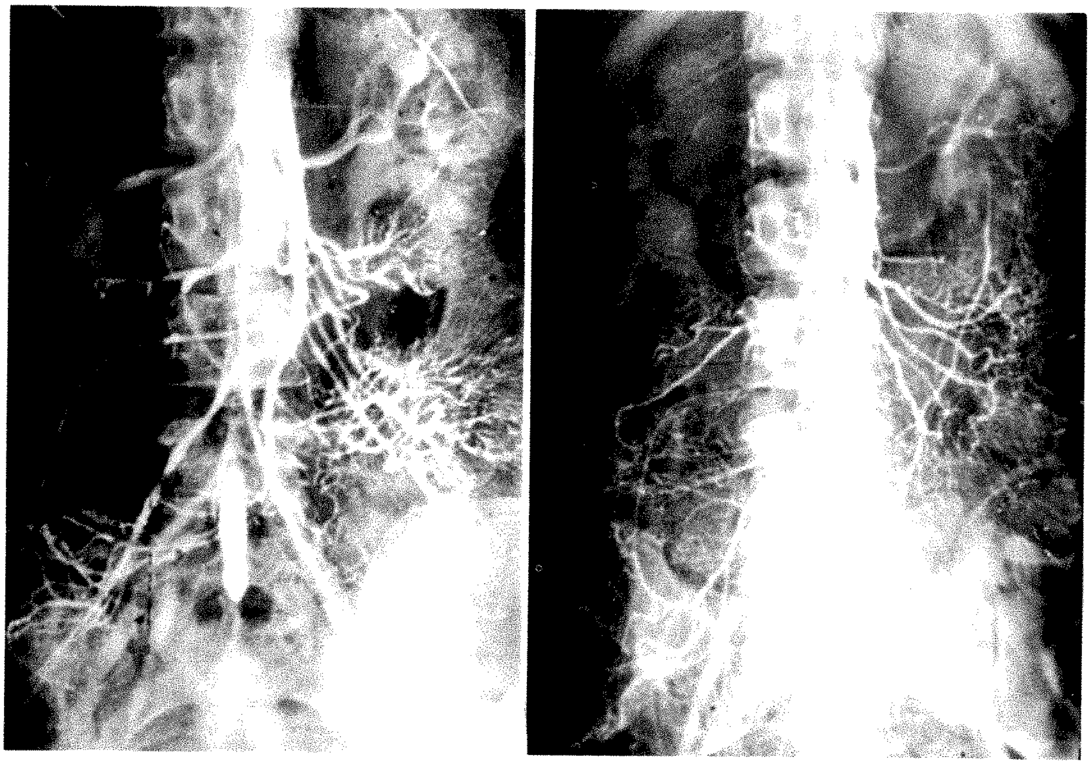

FIG. 3a (Left). Superior mesenteric arteriogram on admission and before treatment. FIG. 3b (Right). Superior mesenteric arteriogram on discharge after recovery. There is adequate circulation with no significant evidence of segmental narrowing. Aortic reflux of dye and dilatation of the proximal vessels are absent.

While attempts to increase cardiac output seem to be a reasonable initial approach to the treatment of this condition, some locally administered dilating drugs must be included in the regimen. The effectiveness of this treatment was borne out in our case not only by arteriographic demonstration of the vasodilator effect of tolazoline hydrochloride and epidural block but also by the temporary abatement of the signs and symptoms, the paucity of the intraoperative pathology and the ensuing uneventful recovery.

Mesenteric vasodilatation has been accomplished both clinically and experimentally in a variety of ways. Isoproterenol, phenoxybenzamine,[18] and tolazoline hydrochloride[1] have been used with varying degrees of success. Although phenoxybenzamine, locally injected into the mesenteric vascular system, fixes to the tissues and therefore has a relatively prolonged local action without systemic effect, tolazoline hydrochloride is equally interesting in that it is both a direct vasodilator and an alpha-adrenergic blocker. It has been used successfully in the treatment of acute vascular insufficiency of the lower extremities as well as of the mesenteric bed.[4] However, since the effect of a single injection is limited to 2 hours, we alternately used another equally effective method of vasodilatation, epidural block, which was proven on arteriography to produce vasodilation. This effect has been documented experimentally[16] and clinically.[13] Splanchnic block has also been reported to be effective in this condition.[6] A possible drawback to the use of tolazoline hydrochloride is that it is also a coronary vasoconstrictor and may therefore be detrimental in elderly patients with coronary artery disease. One of the authors (S.B.) has used papaverine hydrochloride in similar clinical situations with success. Since papaverine is not a coronary vasoconstrictor but is a potent splanchnic vasodilator, we would presently recommend its use. It is possible that glucagon, which increases both cardiac output and mesenteric flow, may also be useful, but this will require clinical evaluation. Another advantage of both papaverine hydrochloride and glucagon is that they may be administered by constant infusion through a superior mesenteric artery catheter.

We also administered antibiotics orally and parenterally because they have been shown to delay or diminish evidence of loss of intestinal viability in cases of vascular compromise.[2,7] A second ancillary measure was the use of oxygen. As this is a reasonable measure in congestive heart failure, it could conceivably have contributed to breaking the vicious cycle of mesenteric vascular spasm secondary to intestinal hypoxia resulting from diminished flow.[6]

When, despite mesenteric vasodilatation, abdominal signs and symptoms reappeared, and the white cell count rose to 20,000/cmm, nasogastric suction was started and the patient was prepared for surgery. The operative findings were encouraging in that there were only short segments of edematous but viable bowel and patent mesenteric vessels. Segmental involvement has been described by others.[1,2,9,11,15]

Nonocclusive mesenteric vascular insufficiency is thought to be a manifestation of splanchnic compensation to low cardiac output. The clinician should have a high index of suspicion in any state of low cardiac output, particularly with unexplained abdominal signs and symptoms. The physiopathologic approach can lead to the proper diagnosis if mesenteric angiography is used. Management should include measures to: 1) increase cardiac output; 2) increase mesenteric vascular flow locally; 3) diminish or delay the occurrence of ischemia; and 4) recognize loss of intestinal viability.

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Resection of Suprarenal Aortic Aneurysm With Autotransplantation of the Kidney

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This is a report of a patient with renovascular hypertension associated with a suprarenal aortic aneurysm that was treated by nephrectomy, resection of the aneurysm and autotransplantation of the kidney. The autografted kidney was preserved on the Mox-100 perfusion-preservation apparatus for over four hours, during which time the aneurysm was resected and replaced with a Dacron bifurcated graft. The authors believe this is the safest method for the management of aneurysms of the suprarenal aorta, especially when associated with renovascular disease, and it deserves wider application in treating major renovascular disease.

THE REMOVAL OF ANEURYSMS that extend above the renal arteries is one of the most difficult tasks the surgeon can undertake. We combined nephrectomy, kidney preservation (on the Mox-100 Perfusion System),[19,20] and autotransplantation of the removed kidney to facilitate the excision and replacement of a suprarenal aortic aneurysm.

Kidney autotransplantation, alone, has been used for the treatment of high ureteral stricture since 1963[14] and for renovascular hypertension in adults since 1965.[8,9,17,18,22,27] The scope of autotransplantation was widened when it was introduced as the treatment of renovascular hypertension in children,[15,25] and for resection of tumors within the renal parenchyma.[4,5,13]

In combination with the accumulated experience and success of kidney preservation,[3,20] autotransplantation is a safe alternative to operative expertise alone in the management of major vascular disorders (suprarenal aortic aneurysms, aneurysms of the renal vessels, and dissecting aneurysms of the aorta with dissection of the renal arteries).

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Case Report

The patient is a 61-year-old-man who was first seen at the University of Minnesota Hospitals in 1966 for a minor injury to the hand. At that time he had a duodenal ulcer with one episode, in 1954, of gastrointestinal hemorrhage.

In 1972 he was readmitted to this hospital with a two-year history of uncontrolled hypertension and a second episode of gastrointestinal hemorrhage in 1971. Aggressive medical treatment controlled his hypertension during his one month hospitalization, and for about six months on an outpatient basis. He was back to the hospital within nine months with uncontrolled hypertension for further evaluation and treatment.

During this last admission and while on high doses of methyldopa, hydralazine hydrochloride, hydrochlorothiazide, and propranolol hydrochloride, his blood pressure fluctuated from 160/80 to 220/120 mm Hg. His BUN was 34 mg/100 ml, and serum creatinine was 2.2 mg/100 ml. His creatinine clearance ranged 30–34 ml/min/1.73 m^2. An arteriogram revealed complete occlusion of the right renal artery and 95% occlusion of the left renal artery. Renal vein renins were 13 ng/ml/hr on the right and 26 ng/ml/hr on the left.

These findings clearly indicated that surgical management was necessary, and that it would be extremely difficult. The laparotomy was through a midline incision. We found that the aneurysm was 12 cm wide at its maximum transverse diameter, and appeared to begin just below the superior mesenteric artery (Fig. 1). After we removed the left kidney with its ureter, the stenotic portion of the renal artery was excised. We flushed the kidney with cold saline before placing it on the Mox-100 perfusion apparatus for preservation (Fig. 2). Following systemic heparinization the aorta was clamped just below the superior mesenteric artery and the aneurysm was incised anteriorly. We removed the laminated clot from inside the aorta and replaced the suprarenal abdominal aortic aneurysm with a 25 mm Dacron bifurcated graft. A long aortoplasty, extending up to the superior mesenteric artery, was necessary to decrease the diameter of the aneurysmal aorta for the aorta-Dacron graft anastomosis (Fig. 3). After the clamps were released and flow was re-established, we proceeded with the standard technique of transplanting the kidney in the right iliac fossa.[24] The kidney had been preserved for 4 hours and 30 minutes.

Because of the previous chronic obstruction of the renal artery, arterial perfusion and flow to the renal parenchyma was temporarily unsatisfactory (for about 10 min). Adequate urinary production was evident, however, before we closed the bladder (Fig. 4). Urinary output during

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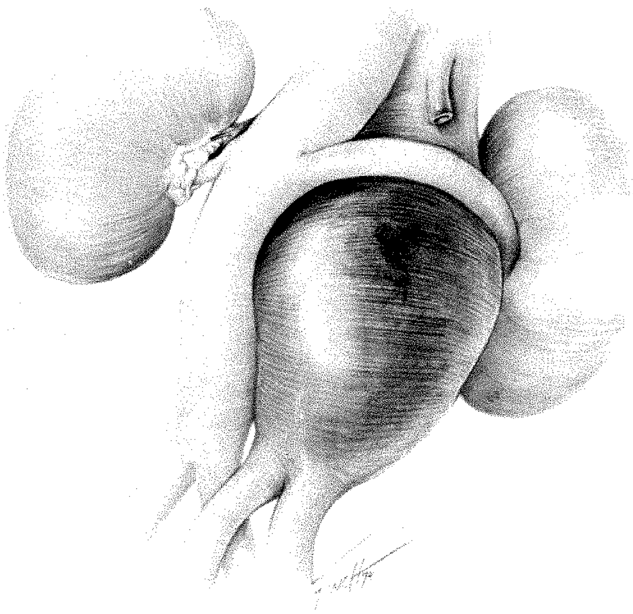

FIG. 1. Position of the aneurysm in relation to the left renal vein and the superior mesenteric artery.

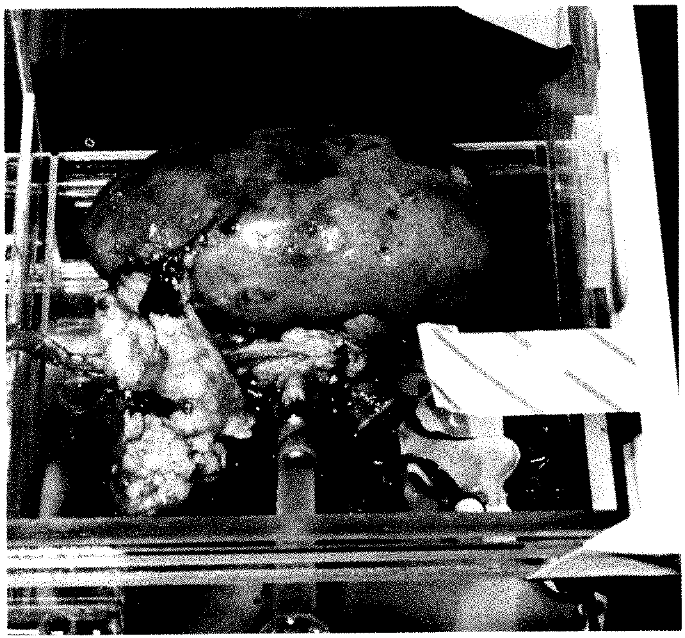

FIG. 2. The left kidney was preserved on the Mox-100 perfusion-preservation machine for 4 and 1/2 hours.

the first 48 hours exceeded 16 liters. The day after surgery the patient's serum creatinine level was 3 mg/100 ml, while his BUN was up to 74 mg/100 ml. At the end of the first week the serum creatinine went down to 1.8 mg/100 ml, the BUN had decreased to 42 mg/100 ml, and the creatinine clearance level ranged from 40–44 ml/min/1.73 m^2. Serial renograms showed progressive improvement of the autotransplanted kidney and an intravenous pyelogram demonstrated a normal collecting system and flow of dye to the bladder.

When the patient was discharged on the 20th day after surgery, his blood pressure was 150/80 mm Hg. At that time he was receiving 250 mg

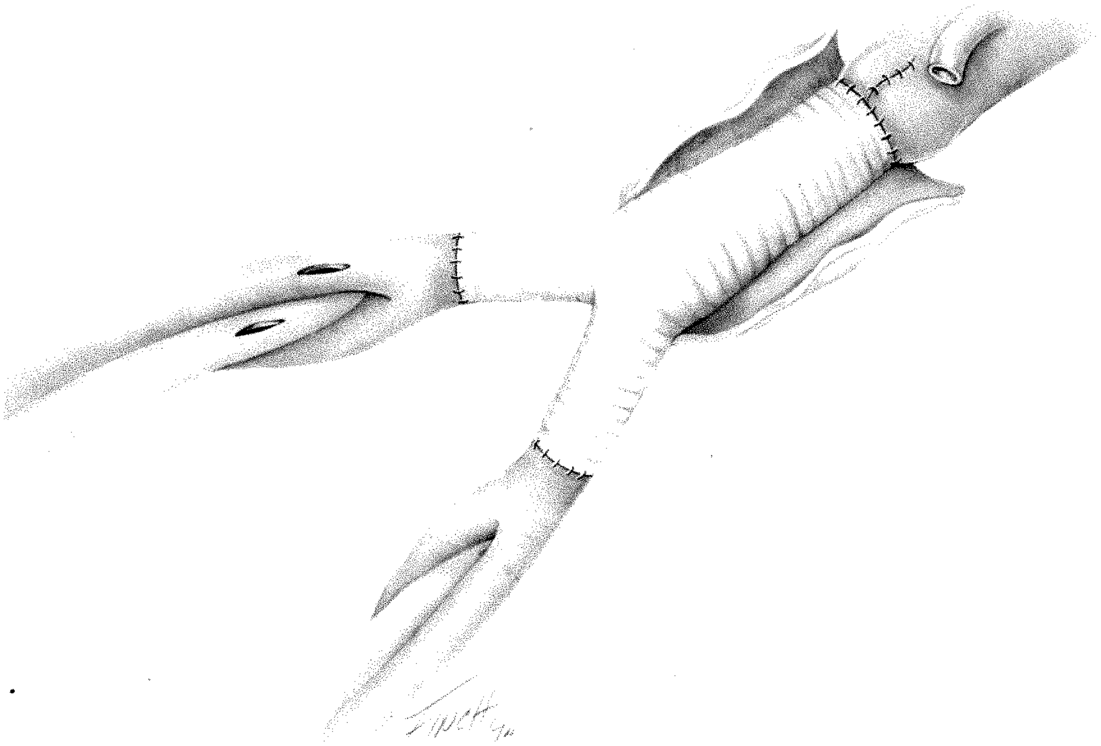

FIG. 3. The aortic aneurysm was replaced by a 25 mm Dacron graft. An extensive aortoplasty was done to reduce the size of the aneurysmal aorta and to facilitate performance of the proximal anastomosis.

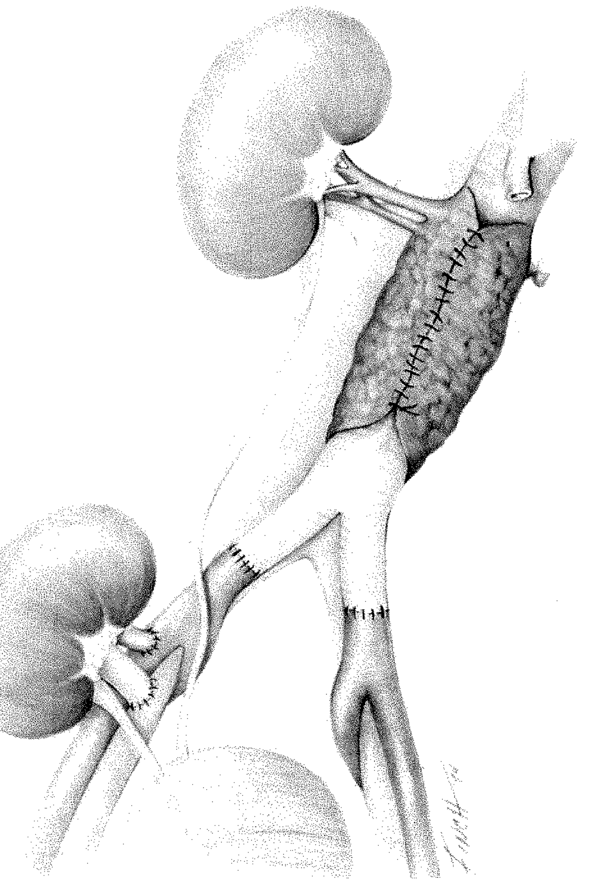

FIG. 4. In the completed procedure the aneurysm has been replaced by a Dacron graft, and the left kidney has been autotransplanted into the right iliac fossa.

of methyldopa three times daily. Currently he requires no antihypertensive medication, and his serum creatinine is 1.4 mg/100 ml, while his BUN is 19 mg/100 ml and creatinine clearance is 44 ml/min.

Discussion

Suprarenal aortic aneurysms are rare. It is estimated that less than 5% of all aneurysms of the abdominal aorta extend above the renal arteries. According to De Camp and Birchall[11] an aneurysm of the abdominal aorta is rarely associated with renal artery stenosis. In the past an aortic aneurysm associated with renal artery stenosis was treated by unilateral nephrectomy, resection and replacement of the aneurysm with an artificial graft.[1] Of course, such treatment is inappropriate if the function of the remaining kidney is inadequate.

DeBakey *et al.*[10] and Garrett *et al.*[12] have reported successful treatment of aneurysms of the thoracoabdominal aorta. In DeBakey's series, 44% of the patients died when the aneurysms were associated with hypertension and renal disease. Although they did not report the causes of death, we assume that acute renal failure of the borderline kidney was the most likely reason for the high mortality in these patients.

Before diuretics like Mannitol and furosemide were available, Sheranian *et al.*[23] reported that renal failure accounted for 20% of their deaths associated with elective aneurysmectomy. Even today acute tubular necrosis is associated with a high incidence of death. Tilney *et al.*[26] reviewed their experience with renal failure after surgical repair of ruptured abdominal aortic aneurysms and reported a 90% mortality.

From our review, we could see that a high death rate results whenever suprarenal aortic aneurysms or thoracoabdominal aneurysms associated with renovascular hypertension are treated conventionally. Recent technical advancements, however, have made available several approaches to concominent problems.

As far back as 11 years ago Hardy[14] introduced autotransplantation for the treatment of a patient with a high ureteral stricture. Before autografting the removed kidney was restored by perfusion with a cold glucose solution. Since then several investigators have modified Hardy's technique.[15-18,21,22,27]

Belzer *et al.*[2] first suggested a new approach to renal autotransplantation in 1970. Their method included flushing the removed dog kidney by gravity flow until the venous effluent was clear, then perfusing the kidney until autotransplantation. Corman *et al.*[9] enlarged on Belzer's approach. In 1973 they reported 3 patients whose kidneys were removed, cooled, perfused with an asanguineous fluid, and studied angiographically in their extra-corporeal state. All of these kidneys were autografted successfully.

Enough experience has been accumulated[3,6] to assure that *ex vivo* hypothermic perfusion is a safe tool for preservation of the kidneys. There is subsequent good renal function even after 24–68 hours of hypothermic perfusion.

We believe that in cases of aneurysms of the thoracoabdominal aorta, suprarenal aortic aneurysms, dissecting aneurysms when the renal arteries are involved, and aneurysms of the renal artery itself, surgical expertise and "heroism" should be avoided. One or, if necessary, both kidneys should be removed and maintained on a perfusion-preservation unit while the vascular lesion is being repaired. Subsequently, when hemodynamics are stable, autotransplantation completes the procedure. This combination of techniques apparently works in the management of renovascular hypertension associated with a suprarenal aortic aneurysm since our patient is well and completely rehabilitated.

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Analysis and Significance of Nosocomial Infection Rates

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An analysis of the systems of nosocomial infection reporting utilized in a 332 bed, urban, referral-type hospital demonstrated that physician reporting was much less reliable than a well-planned surveillance system coördinated by an infection control nurse. During 12 months' experience with the most recently devloped system, the average monthly rate of nosocomial infection was 10.7%. A prevalence survey gave a rate of 14.4%. The efficiency of reporting was close to 100% when the infection control nurse spent 100% of her time on surveillance. With a reduction in surveillance time to 75%, the efficiency of reporting fell to about 75%.

NOSOCOMIAL INFECTION represents a potentially serious problem for all hospitalized patients. The incidence and character of infections vary among hospitals of different types and sizes as well as within a particular hospital at different times of the year. Before appropriate measures can be taken to control nosocomial infection, a reliable reporting system must be instituted in order to determine the true magnitude of the problem. A falsely low infection rate generated by a poor reporting system may result in a complacent attitude toward controlling infection in a particular hospital.

The Graduate Hospital of the University of Pennsylvania is a 332 bed, university-affiliated hospital without pediatric or obstetrical services. The Infections Committee has accumulated statistics on nosocomial infection since its inception in 1958. This article evaluates and compares the methods of infection reporting employed during a 15-year period (1958–1973).

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Methods

Physician Reporting

Between 1958 and 1966 an infection report form was completed by the attending physician, house officer, or nursing staff. This voluntary reporting system emphasized staphylococcal infections. The office of the hospital director reviewed the infection reports and sent them to the members of the Infections Committee for examination on a monthly basis. In 1966 a revised infection report form became a part of every patient's chart with mandatory completion at the time of discharge.

Surveillance Program

In October 1970 an infection surveillance program was instituted with a fulltime infection control nurse as coördinator. Because baseline information was needed to determine what kinds of problems existed at the Graduate Hospital, the nurse spent 100% of her time on surveillance during the initial months of her employment. She collected infection information according to a standard pattern and classified infections according to the guidelines issued by the Center for Disease Control.[6] The infection control nurse analyzed and summarized the data for monthly review by the Infections Committee. The initial recording system consisted of cards manually coded to indicate type and hospital distribution of infection. After five months this method was replaced by a McBee punchcard system which used cards specifically designed for the program. It became apparent, however, that the infection control nurse was accumulating massive amounts of data that generated extensive clerical work and could not be summarized in a reasonable amount of time. After a pilot study on urinary tract infection[10] proved successful, a computer-assisted surveillance program for recording all nosocomial infections

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was initiated in April 1972. The reliability and accuracy of this infection surveillance system were supported by an infection prevalence study performed on June 19, 1973.

Results

The average nosocomial infection rates resulting from the different reporting systems are shown in Fig. 1. During the period of physician reporting, the rate was 1.3%. After the introduction of an infection control nurse who spent 100% of her time on surveillance, a tenfold increase to 13.2% occurred. During the second year of the surveillance program, when an additional part-time nurse was assigned to collect all data on urinary tract infections, the total infection rate again rose to 16.7%. A decrease in the reported rate to 10.7% occurred during the final year of the program, when the infection control nurse spent approximately 75% of her time on surveillance.

On June 19, 1973, the hospital census was 243 patients. Upon review of all charts, 35 nosocomial infections were found, giving an infection prevalence rate of 14.4%.

Discussion

Nosocomial infections are of great clinical and epidemiologic significance. Recently, there has been a surge of interest in nosocomial infection among physicians and hospital administrators, not only because of increasing morbidity and mortality rates but also because of financial and legal complications. Alexander[3] estimates the annual attack rate for nosocomial infections to be 6.3% of all hospital admissions. This, then, involves 2 million Americans per year and exceeds traffic accidents and the leading cancers in morbidity and mortality.[3] The financial loss to the public due to wound infections alone is estimated to be almost 10 billion dollars per year.[3]

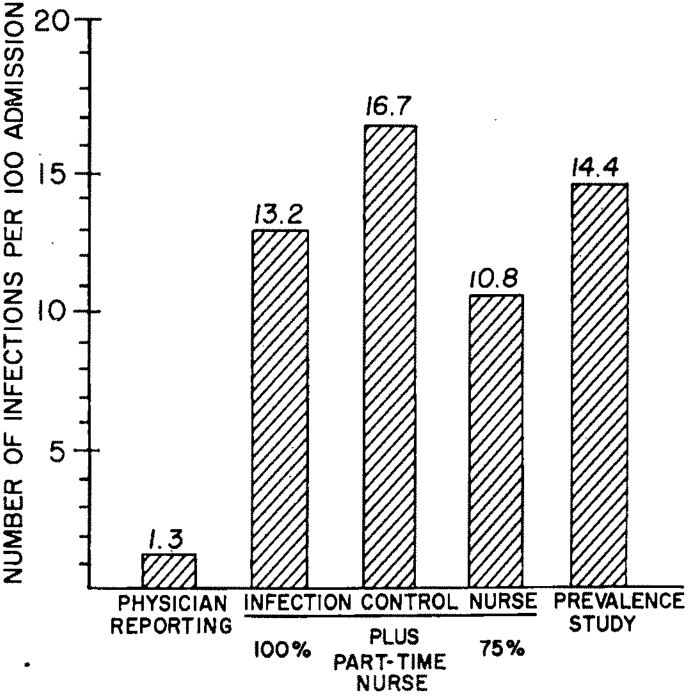

FIG. 1. Average nosocomial infection rates resulting from different reporting systems, 1958 to 1973.

The epidemiology of these infections is complex and in continual flux. With the widespread use of antimicrobials, resistant microorganisms have arisen. Numerous advances in medicine and surgery have created populations of more susceptible patients. In recent years gram negative bacilli have replaced gram positive staphylococci as the predominant causative organisms,[1,4] with a concomitant increase in morbidity and mortality. There is little doubt that surveillance of nosocomial infections is extremely important in order to properly assess endemic rates of infection, detect epidemic levels rapidly, and evaluate the effectiveness of various infection control measures.

The initial attempt in our hospital to record nosocomial infections was inadequate, yet this physician reporting system was accepted for 12 years. The classification of infections was primitive and fragmentary. Different physicians had varying opinions of what constituted an infection. The chore of filling out another chart sheet was time consuming, retrospective, and sometimes self-incriminating. There were serious discrepancies between the bacteriological information, verbal reports on patients, and completed forms. No one person was responsible for coordinating all infection information. Inaccuracies predominated. The reported infection rate during this 12-year period averaged 1.3%. Even with the institution of a mandatory physicians' report in 1966, reported infection rates ranged from 0.6% to 2.5%.

One might question our conclusion that this reporting system was unreliable and inaccurate. However, during this period the Infections Committee was interested primarily in one type of infection, i.e., staphylococcal surgical wounds, and consequently few other infections were reported. Therefore, the overall infection problem in the hospital was never completely recorded. Furthermore, in 1971, after a surveillance program had been initiated, the reliability of the physician reporting method was tested during a two-month period and compared to formal infection surveillance. The physician reporting system gave an infection rate of 1.5%, whereas the infection control nurse reported a rate of 13.2%.

A study performed at Johns Hopkins Hospital[6] indicates that even when physicians are required to report only one type of nosocomial infection, the system may provide an inadequate indication of this particular infection problem. During the period 1960–61 physicians were required to report only staphylococcal infections. In addition, a member of the infection control committee visited all patients having cultures positive for coagulase-positive staphylococci in order to verify the presence of a nosocomial infection. During the period of the study physicians reported 64% of the staphylococcal infections detected by the bacteriological reports and followup ward visits. By individual service the accuracy of this system of physician reporting ranged from 47% to 100%, and there was an even greater monthly variation (20–100%).

Our three-year experience with an infection surveillance system demonstrated that, given effective methods of collecting, recording and reporting infection information, a fulltime infection control nurse can provide a reliable and valuable report on nosocomial infections. The nurse worked in close association with the hospital-appointed epidemiologist who chaired the Infections Committee. She collected information according to a standard pattern. Reports of all positive cultures were obtained daily from the bacteriology laboratory, and the charts of these patients were reviewed to verify infections. Charts were also scanned periodically for signs of infection such as elevated temperature, changes in vital signs, and elevated white blood count. There was continual communication with physicians concerning specific infection problems. Frequent ward rounds with the nursing staff often revealed occult infections. A considerable amount of the nurse's time was spent in geographic problem areas of the hospital. Patients known to be susceptible to infection were followed closely. With these techniques, few infections went unnoted.

During the urinary tract infection pilot study,[10] when surveillance of urinary tract infection was intensified and a part-time nurse collected all data on these infections with computer analysis and reporting, the reported total infection rate increased to 16.7%. This result demonstrates how the reported rate can be pushed even higher by intense interest and even possible overinterpretation of the problem. During this period multiple urinary tract cultures were often performed during one episode of infection and any change in organism or antibiotic sensitivity was reported as a new infection. Therefore, multiple urinary tract infections were recorded when in a general surveillance program a single infection might have been reported.

As the infection control nurse became better known and more experienced, other duties in addition to surveillance were expected of her, such as lecturing, educating hospital personnel, increasing awareness of the benefits of hospital surveillance, and educating herself in mechanisms of infection control and prevention. Time-consuming consultations on specific infection problems were more numerous, as were regular meetings and responsibilities outside the hospital. During the final year of the surveillance program the infection control nurse estimated that only 75% of her time was being spent on surveillance, and concomitantly the reported infection rate decreased to 10.7%.

Three successive systems of recording, analyzing and reporting infection data were utilized. Initially, infection data were recorded on index cards, which were coded to indicate the type of infection and filed according to floor. This system was clumsy and required that cards be studied individually when compiling a monthly report. The McBee punchcard system greatly facilitated retrieval of information on a daily, weekly, or monthly basis and reduced the time spent in compiling statistics. In the final computerized system the McBee punchcard was replaced by an information sheet designed to include more adequate information for investigation of hospital-acquired infection along with contributory indices necessary for a complete epidemiologic evaluation. The information sheets were checked for errors at the end of the month and submitted to the data processing department, where a five-page report was generated for distribution to the Infections Committee. This computerized reporting system saved the infection control nurse five hours a week previously devoted to recordkeeping, as well as several days each month spent preparing the monthly infection report.

To evaluate the accuracy of a nosocomial infection reporting system, a prevalence survey[7] should be performed. Comparison of the prevalence rate to the monthly or yearly infection rate will shed light on the overall efficiency of reporting. Our prevalence rate on June 19, 1973, was 14.4%. During this period the infection control nurse was spending approximately 75% of her time on surveillance and was reporting an average rate of 10.7%. Therefore, the efficiency of our surveillance system was approximately 75%. Prior to this period, when the nurse spent 100% of her time on surveillance, the average yearly rate was 13.2%, which probably represented an efficiency of 90% or better.

Accurate infection reporting is essential for comparative purposes. Rates reported by various hospitals often reflect differences in the accuracy of the respective reporting systems rather than in the actual incidence of infection. If the monthly or yearly reported rate is adjusted to a more accurate level according to the results of a prevalence survey,[7] it may be considered an accurate indication of the actual incidence of nosocomial infection within the hospital. Some community hospitals report adjusted rates in the low range of 1.1–4.8%.[7] On the other hand, large urban referral hospitals report prevalence rates as high as 11.5–15.5%,[1,2,4,8,9,11] and the rates generated by our surveillance system fall within this range. One reason for the difference in the incidence of nosocomial infection in the two types of hospitals may be that the more chronic and complicated cases are often referred by the community hospital to the larger urban hospital, where more complete diagnostic workups and more intensified treatment programs can be instituted. In addition, the number of infected patients and the availability of organisms commonly associated with nosocomial infection may be higher in urban and university-affiliated hospitals.

An "acceptable" nosocomial infection rate is therefore difficult to define. It is each hospital's responsibility to report as many nosocomial infections as possible in a clear,

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concise, and up-to-date manner so that responsible individuals can logically cope with infection problems. The value of a well-organized and active nosocomial infection surveillance program cannot be overemphasized. Prerequisites for a successful program include an interested hosptial administration, an infection committee representing the major medical departments and hospital services, an active microbiology laboratory, an infection control nurse, and an efficient system of collecting, recording, analyzing, and reporting data on nosocomial infections. All hospital personnel must support such a program and respond collectively to reduce high infection rates.

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Erratum

By a transposition of lines, the article by P. R. Baker and R. Shields on page 89 of the July 1974 issue of Annals of Surgery was incorrectly titled. The title should read "Effect of Portacaval Transposition on Hepatic Blood Flow During Obstruction to the Venous Outflow from the Canine Liver."

Granulomatous Peritonitis Due to Cellulose Fibers From Disposable Surgical Fabrics:

Laboratory Investigation and Clinical Implications

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Two patients with postoperative granulomatous peritonitis were found to have lesions with a distinctive type of foreign body. Laboratory investigation revealed this foreign body to be cellulose, morphologically identical with fibers derived from disposable surgical gowns and drapes, and cotton. The same type of foreign body granulomas was produced experimentally by introducing lint prepared from these gowns and drapes into the peritoneal cavities of rats. Since disposable gowns and drapes are being used with increasing frequency, cellulose lint derived from these sources should be added to the list of hazardous foreign materials which are potential wound contaminants.

Iatrogenic foreign body contamination of the peritoneal cavity may produce granulomatous peritonitis with well defined clinical and pathologic characteristics.[2,7] Glove lubricants have been found responsible for many examples of this entity, thus lycopodium[1] and talc[3,9] were incriminated and replaced by starch powder. Although at first considered innocuous,[8] it too was found capable of causing the same syndrome.[2,6,7,10,12]

Two of our patients, displaying the clinical picture of intra-abdominal abscess, were found at laparotomy to have foreign body granulomas containing doubly refractile, trilaminar-appearing fibers but no starch granules. The morphology of the fibers was identical with that of cellulose fibers and quite different from that of silk or catgut sutures.

The observation that the shaking and handling of disposable surgical gowns and drapes made from nylon or rayon supported cellulose wadding releases a considerable amount of lint into the air, led us to examine this material microscopically. It was found to have the structure of cellulose fibers and was identical to the fibers found in our two patients. An identical granulomatous peritonitis was produced experimentally by introducing the lint from these fabrics into the peritoneal cavity of rats.

Our purpose is to report the occurrence of such lesions in a group of patients from the Department of Surgery of the Long Island Jewish-Hillside Medical Center-Queens Hospital Center Affiliation and to correlate them with the lesions created in our experimental animals.

Case Reports

Case #1 B.B. A 37-year-old black male was admitted on January 26, 1972 to Queens Hospital Center with signs and symptoms of partial intestinal obstruction. Barium enema demonstrated a constricting lesion of the ascending colon and on February 4 a right hemicolectomy and ileo-transverse colostomy were performed for a non-perforating adenocarcinoma. The patient had an uneventful postoperative course and was discharged on February 14. He was readmitted on February 24 with a four-day history of diffuse abdominal pain, anorexia and a low grade fever. On physical examination his abdomen was slightly distended with diffuse tenderness, most marked in the right lower quadrant where an ill-defined mass was palpable. During two weeks of observation, his rectal temperature was 37.8–39.2 C. A mild leukocytosis with eosinophilia was present. On March 10 an exploratory laparotomy was performed for suspected intro-abdominal abscess. Minimal amounts of straw-colored fluid were present, but no abscesses were found. The entire peritoneum including the mesenteric and bowel surfaces were studded with grey-white nodules varying 2–5 mm in diameter, associated with thick omental adhesions. This was thought to represent diffuse carcinomatosis. Biopsies revealed an organizing panniculitis showing fibrous tissue, lymphocytes, eosinophils and noncaseating foreign body granulomas which contained fiber-like, curved, doubly refractile trilaminar inclusions. (Figs. 1 and 2) Postoperatively, his fever subsided, and he was discharged on March 27. Cultures of the peritoneal fluid showed no bacterial growth.

Case #2 M.M. A 16-year-old black male was admitted on March 10, 1973 to Queens Hospital Center with a stab wound in the left upper quadrant of the abdomen. Exploratory laparotomy failed to reveal any intra-abdominal injury. His postoperative course was uneventful and

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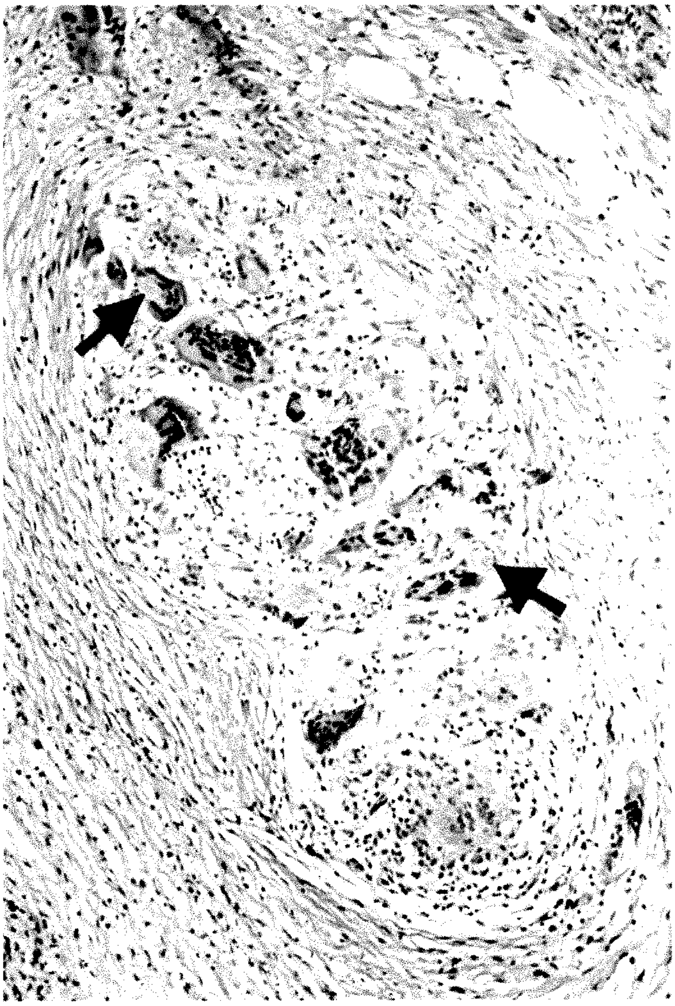

FIG. 1. Case I. Typical granuloma composed of giant cells, macrophages, eosinophils and lymphocytes, with foreign body inclusions (arrows) and surrounding fibrosis (H & E ×50).

he was discharged on March 17. Three days later he was readmitted with abdominal pain, distention and fever. On physical examination there was diffuse abdominal tenderness, most marked in the area of the stab wound which was indurated. It was elected to observe the patient. His temperature ranged 37.8–38.9 C associated with a mild leukocytosis and eosinophilia. The findings persisted and on April 30 his abdomen was explored for a suspected intra-abdominal abscess. At laparotomy the entire peritoneal surface was covered with grey-white nodules. Multiple adhesions were present between loops of bowel, omentum and the abdominal wall. No abscess cavity could be found. Biopsy of a peritoneal nodule, revealed a foreign body granuloma containing the same fiber-like inclusions seen in Case I. (Figs. 3 and 4) Postoperative treatment included Prednisone, 5 mg P.O. every six hours. The fever subsided and he was discharged on May 8. Cultures of the peritoneal fluid revealed no bacterial growth. On May 18 he was readmitted with a clinical picture of partial intestinal obstruction which was successfully treated by intestinal decompression.

Comment

In both cases, the patients were draped and the operating room personnel gowned with disposable fabrics manufactured from nylon supported cellulose fibers. We have subsequently identified eight additional patients in whom foreign body granulomas were found which contained the fiber material. In five patients, the foreign bodies were in soft tissue and of little clinical significance. Three patients, however, required re-operation for intestinal obstruction.

Experimental Methods and Materials

0.6 × 1.5 meter polyethylene bags were rinsed with 500 cc of distilled water and dried. They were then half-filled with sterile disposable gowns and drapes, closed and shaken for half an hour. After the fabric was removed, the remaining lint was collected and sterilized with ethylene dioxide.

Ten mature Sprague-Dawley rats of both sexes were anesthetized with subcutaneous nembutal, their abdomens shaved and prepped with povidone-iodine solution and draped using disposable drapes of the same fabric as those used to provide the lint. The surgeons were gowned with the same fabric and their gloves were carefully washed with normal saline solution until all visible starch was removed. A midline laparotomy incision measuring 1.5 cm

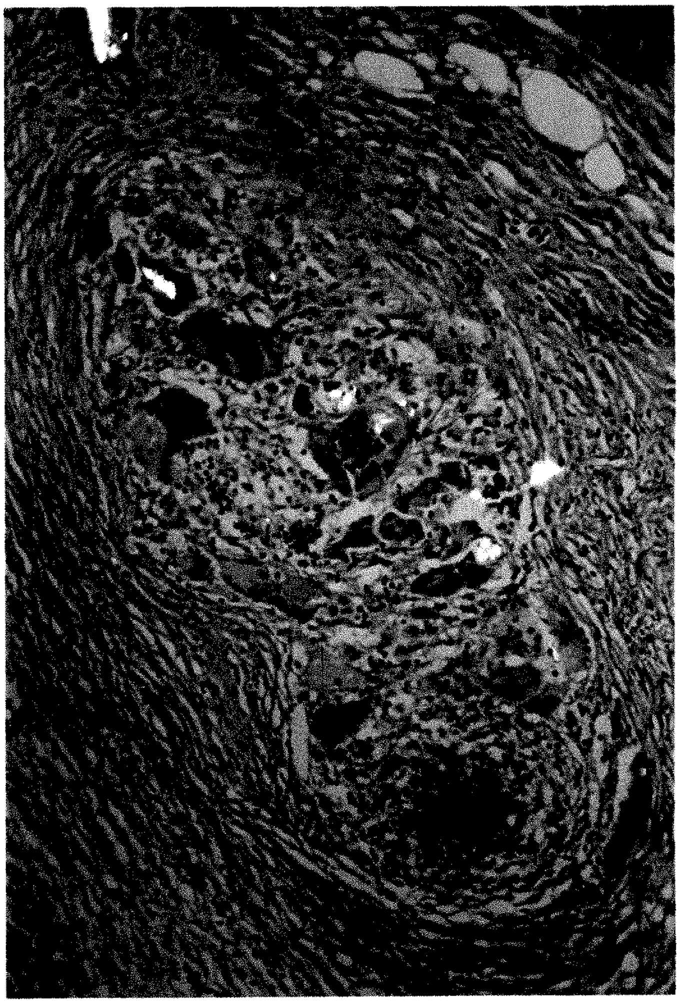

FIG. 2. Case I. Same field as Fig. 1 showing inclusions within giant cell under polarized light (H & E, and polarized light ×50).

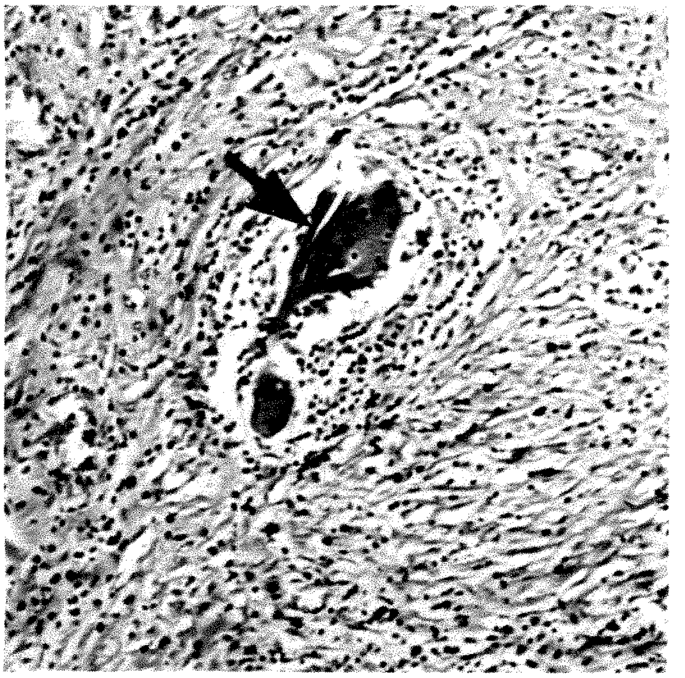

FIG. 3. Case II. Giant cell containing fiber split to produce "forked tongue" appearance (arrow) (H & E ×50).

was performed on each animal and a 2 mm square pledget of the lint was inserted into the peritoneal cavity which was then closed in layers with 4-0 silk.

In a second group of ten rats, lint collected in the same manner from cotton laparotomy pads was introduced into the peritoneal cavity. A third group of ten animals was subjected to the same procedure except that no lint was introduced.

Two animals from each group were sacrificed by decapitation at 1, 5, 6, 9 and 13 days. The peritoneal cavity was entered through an incision remote from the previous one and the appearance of the abdomen noted. The areas with gross pathology were biopsied and microscopic sections prepared.

The following techniques were used to stain the tissue, identify the fiber structure and differentiate it from other fibrous materials: 1) hematoxylin and eosin; 2) periodic acid schiff; 3) chlorzinc iodide; 4) cyanin-erythrosin stains; and 5) polarized light microscopy. In addition, specimens of raw lint and cotton were examined microscopically both unstained with polarized light and stained as described above.

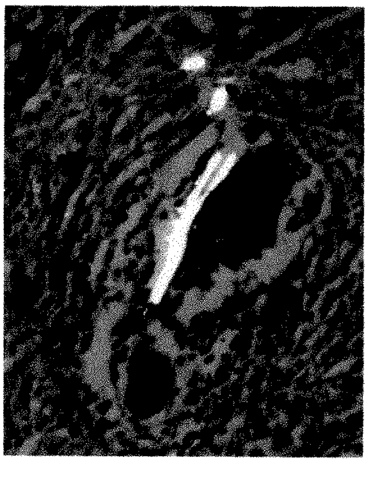

FIG. 4. Case II. Split fiber seen in Fig. 3 under polarized light (H & E, and polarized light ×80).

Results

Necropsy of animals from groups one and two revealed nodular adhesions between the omentum and the anterior abdominal wall in the area where the lint had been implanted. Microscopic examination of the tissue from the serially sacrificed animals revealed the sequential development of typical foreign body granulomas containing the characteristic fiber inclusions.

Twenty-four hours after implantation, fibers of variable length were suspended in edema fluid with a demarcating zone of polymorphonuclear leukocytes. By the fifth day, fibrin and polymorphonuclear leukocytes were abundant, and surrounded by granulation tissue (Fig. 5). Subsequently, a few foreign body giant cells appeared and by the ninth day, noncaseating granulomas were well formed with the giant cells containing the fibers. Interstitial fibrosis appeared by the thirteenth day (Fig. 6). The foreign body granulomas have the same general appearance as the biopsy specimens from cases I & II (Figs. 1–4), with the additional presence in the human lesions of significant numbers of eosinophils. Animals from the third group revealed no intra-abdominal gross pathology.

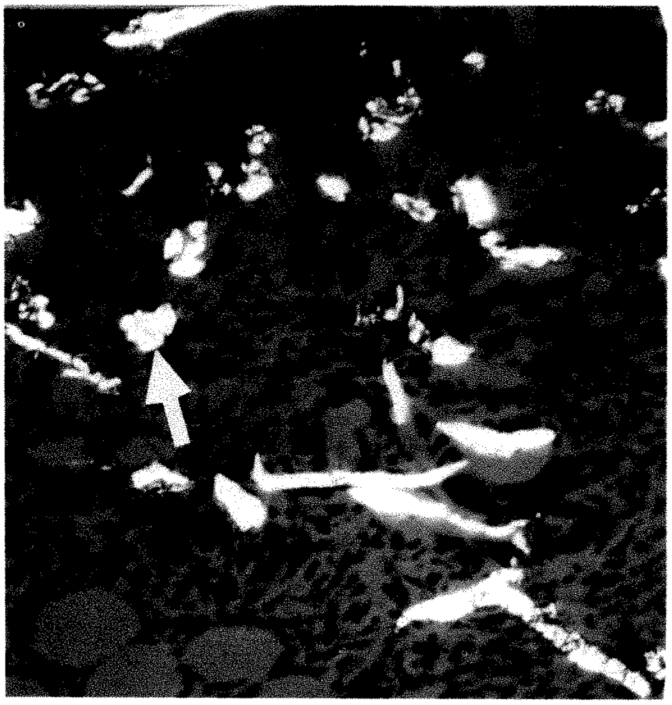

FIG. 5. Rat tissue, five days after implantation, showing fibers. Note trilaminar structure, transverse folds and doughnut configuration (arrow) (H & E polarized light ×50).

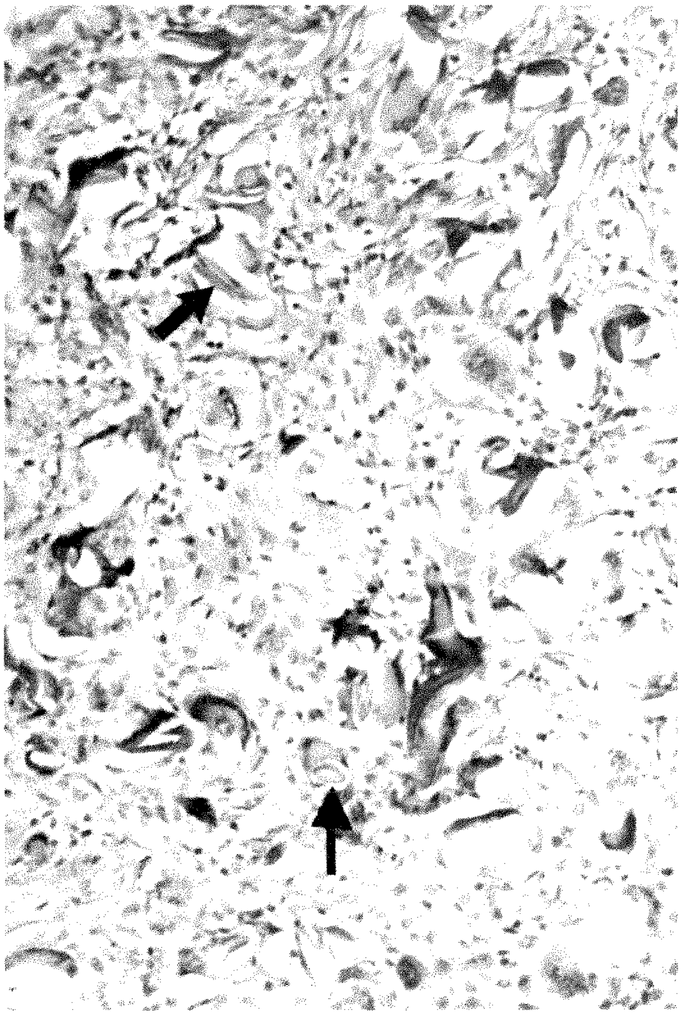

FIG. 6. Rat tissue 13 days after implantation showing numerous "forked tongue," trilaminar and doughnut configurations of the fibers in giant cells (arrows) (H & E ×80).

The unstained fibers range 5–15 μ in width and up to several hundred μ in length. They are bent at many levels demonstrating obliquely transverse folds. A trilaminar appearance is seen with three apparent layers extending in the longitudinal direction; the two outer layers are dense with a central lumen. The structure is doubly refractile with polarized light and exhibits dichroism, changing from port wine color to prussian blue when the polarizing lens is rotated (Fig. 7).

In both human and rat tissue sections the fibers are present as variable short segments approximately 100 μ in length, owing to sectioning for microscopic preparation. They are seen in transverse section to be irregularly ovoid with an empty central lumen resembling an elongated doughnut. They are also seen to have been partially split longitudinally producing a "forked tongue" appearance in tissue. In all other respects they are identical with the untreated lint described above.

The fibers from both cotton and the disposable fabrics have the following staining characteristics whether in tissue sections or mounted on a slide. They stain pink with H & E, are PAS positive, diastase resistant, and are positive with chlorzinc iodide (consistent with carbohydrate). With the cyanin-erythrosin stain, the fibers from both sources stain pink, confirming their cellulose content. In addition, larger diameter fibers from the disposable fabrics stain blue, indicating the presence of lignin.[4] The larger fibers constitute about 20% of the sample.

Discussion

Our findings demonstrate that lint emanating from disposable gowns and drapes can produce a peritoneal reaction. This response is characterized clinically by signs and symptoms of acute peritoneal irritation and histologically by a giant cell foreign body granuloma containing fibers

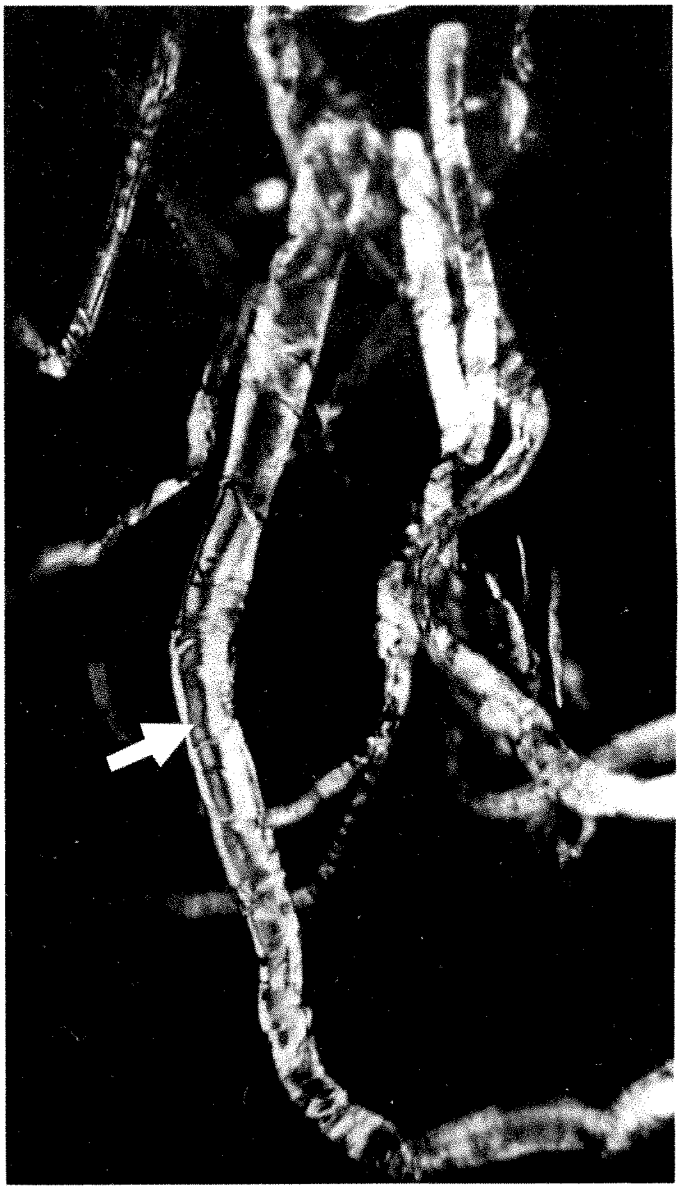

FIG. 7. Unstained fiber from disposable fabric under polarized light. Note trilaminar structure and obliquely transverse folds. Arrow indicates dark zone which shines brilliantly prussian blue in color preparations, with contrasting reddish zone (polarized light ×80).

indistinguishable from the material obtained from the disposable, non-woven fabrics. In our experimental animals, similar lesions were reproduced by the intra-peritoneal implantation of this material.

Non-woven disposable gowns and drapes are fabricated from cellulose wadding bonded to a nylon or rayon scrim. The source of the cellulose incorporated in the disposable fabric is at least partially from wood, as indicated by the presence of lignin in approximately 20% of the untreated fibers, predominantly those of larger diameter. Cotton contains no lignin.[13] The disposable fabric lint, as prepared manually and implanted in rats, is seen in the tissue to contain the large diameter, lignin positive fibers. However, in the human tissues, not only were the fibers few in number, but the fragments of fibers encountered were predominantly of small caliber and not positive for lignin. Presumably, the smaller fibers are more readily loosened and shed from the non-woven disposable fabric. They can thus be disseminated in the air, picked up on instruments or, by direct contact, contaminate the peritoneal cavity.

The fibers observed in the granulomas demonstrate the morphologic criteria of cellulose vegetable fibers: they exhibit a trilaminar structure, transverse folds and, on cross section, demonstrate an irregular ovoid configuration with a central lumen. Classically, wood fibers are described as having nodes or junctions which appear as transverse folds. These are absent in cotton fibers.[5,13,14] In microscopic sections, however, it has been impossible to differentiate cotton from cellulose fibers of wood origin by morphologic criteria, because the cotton undergoes artifactual bending within the tissues.

Despite the widespread use of disposable surgical fabrics, only a few of our patients have reacted to this form of lint and developed recognizable complications. The presence of leukocytosis with eosinophilia and the prevalence of eosinophils in the foreign body granulomas suggests an allergic or hypersensitivity reaction which warrants further investigation. A similar mechanism has been postulated with respect to starch peritonitis.[2,7,15]

Of concern is the fact that cellulose is not normally broken down by human enzyme systems and one may not anticipate that foreign body lesions due to cellulose fibers will resolve in time, as do starch granulomas.[2,6,7] The future course of such patients is not known. We do not know if diagnostic paracentesis would have been of help in these patients[15] since they had little ascitic fluid and no starch granules were found on microscopic examination of the tissues.

Most of the materials left in tissue by the surgeon, whether accidentally or purposefully, produce a characteristic reaction. The response to various suture materials and glove lubricants is well known. Woven cotton laparotomy pads, gowns and drapes have been used for decades without widely recognized untoward effects, although gauze pads have been implicated in the formation of adhesions.[11,16] In our patients, we could not identify any of the known elements. The only foreign bodies which could be identified were cellulose fibers. Since these foreign bodies are so striking to the pathologist, one would expect them to have been described and well recognized many years ago, if indeed they were produced by shedding from cotton fabrics. The ability of lint from the disposable fabrics to elicit an identical foreign body reaction was demonstrated in our animal experiments. We believe this adds another etiologic agent to the list of foreign materials which are potentially hazardous to our patients.

Acknowledgment

We gratefully acknowledge the help of Stanley H. Shapiro M.S. in performing the various special staining techniques used in this investiation.

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Spigelian Hernia

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Nine cases of Spigelian hernia treated during a period of five years are presented. The literature is reviewed and the importance of recognizing the condition is stressed. The main pathological and clinical features are discussed.

HERNIA of the semilunar line or Spigelian hernia is uncommon. Its true incidence is probably greater than the relatively small number of patients reported in the literature, due to failure to recognize the clinical picture. Nine patients with this lesion seen during the past five years are presented, with stress on the clinical and morphological aspects, and a review of the literature of this anomaly.

Case Reports

Case 1. A 44-year-old woman was admitted for a mass in the left lower quadrant of 16 months duration. A round mass 8 cm in diameter was felt in the left lower quadrant. A direct inguinal hernia was diagnosed. At operation a Spigelian hernia was found beneath the intact external oblique aponeurosis. The hernial orifice measured 2 cm. The sac was excised, the muscles closed in layers and the external oblique aponeurosis was imbricated. The postoperative course was uneventful.

Case 2. The patient was a 69-year-old woman. She had a mass in the left lower quadrant for seven years, and steadfastly refused surgery. She was admitted after an episode of incarceration and operated on with a diagnosis of inguinal hernia. A small indirect inguinal hernia was found. 4 cm cephalad to the inguinal canal another hernial sac was seen protruding through the fibres of the internal oblique and transverse muscles and through the attenuated fibres of the external oblique aponeurosis, lying in the subcutaneous fat. The hernial ring was in the semilunar line. Both sacs were excised, the upper defect was closed in layers, the inguinal canal was reinforced by a Bassini repair and the external oblique aponeurosis was imbricated. The patient recovered smoothly.

Case 3. A 59-year-old obese woman was admitted to the medical service for evaluation of recurrent right lower abdominal pain. She had undergone several operations in the past (cholecystectomy, repair of umbilical hernia, ectopic pregnancy and appendectomy). During the previous two years she had been complaining of recurrent colicky pain and fullness in the right lower abdomen. On examination an ill-defined round and tender mass 10 × 10 cm was palpated in the right lower quadrant. A barium swallow demonstrated a loop of small bowel protruding through the abdominal wall (Figs. 1 and 2). A diagnosis of postoperative hernia was made and, because of a sudden episode of strangulation, the patient was operated in emergency. At operation a Spigelian hernia was found, the sac lying beneath the external oblique aponeurosis and the hernial orifice situated in the semilunar line at the point of origin of the semicircular line, well away from the previous laparotomy scars. The sac contained a strangulated but viable loop of small bowel. The hernia was repaired in the usual manner and the patient recovered.

Case 4. A 49-year-old woman presented with a left lower quadrant mass. It had been present for three years and was painful at times. On examination a 10 × 10 cm mass was found in the left lower quadrant and diagnosed as a Spigelian hernia. The diagnosis was confirmed at surgery and repair was performed as above. The postoperative course was smooth.

Case 5. A 69-year-old woman was admitted for a right lower quadrant mass of several years duration. At age 30 she had undergone a gynecological operation through a transverse suprapubic incision. The mass was occasionally painful. Physical examination revealed an oblong mass 10 × 6 cm in diameter in the right lower quadrant lateral to the rectus border at the level of the anterosuperior iliac spine (Fig. 3). A Spigelian hernia was diagnosed and confirmed at operation. The sac contained a loop of small bowel. The sac was excised, the muscles closed in layers and the aponeurosis imbricated.

Case 6. A 61-year-old man had been operated for perforated appendicitis 20 years before. He had vague abdominal complaints for some time and two months before admission he felt a lump in the right lower abdomen. On examination a 7 × 7 cm mass was palpated laternal to the appendectomy scar. The diagnosis of Spigelian hernia was confirmed at operation. The hernial orifice was not related to the previous appendectomy scar, lying in the semilunar line, in otherwise healthy tissue. The hernia was repaired in the manner described above, which by now has become routine.

Case 7. A 52-year-old man was admitted for a left lower quadrant mass which had been present for three months. An oval mass 9 × 4 cm in diameter was felt in the left lower quadrant. A Spigelian hernia was diagnosed. At operation a large arterial branch originating from the deep epigastric artery was found emerging through the hernial orifice. The sac contained the sigmoid colon. The hernia was repaired.

Case 8. A 48-year-old woman presented with signs of small bowel obstruction. She had had a Caesarian section performed 17 years before. On examination a tender mass measuring 12 × 12 cm was found in the right lower quadrant. The patient was operated on and the diagnosis of

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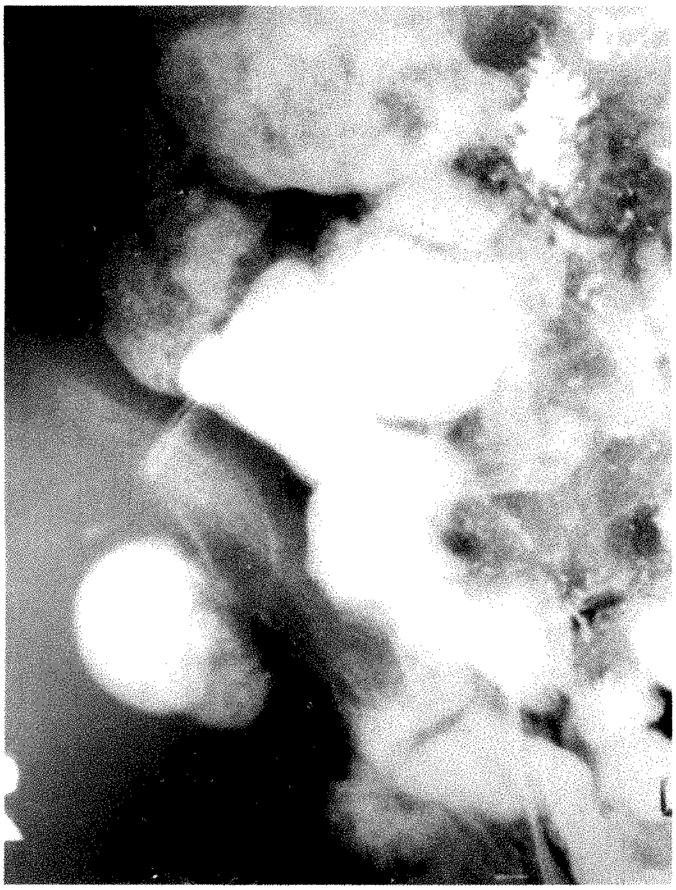


FIG. 1. Case 3. Barium swallow showing loop of small bowel outside abdominal cavity.

incarcerated Spigelian hernia confirmed. The sac contained a loop of small bowel. In this case also a major branch of the deep epigastric artery was found passing through the hernial ring. The bowel was returned to the abdomen, the sac excised and the abdomen repaired in the usual manner.

Case 9. A 66-year-old woman was admitted for a right lower quadrant mass of several months duration. In the past she had undergone umbilical hernia repair and two right inguinal hernia repairs. A Spigelian hernia was diagnosed and confirmed at surgery. The sac was empty and the routine repair was performed.

Discussion

Anatomy and Pathology

Spigelian hernia (also known as "spontaneous lateral ventral hernia,"[6] "hernia through the conjoint tendon,"[12] "hernia of the semilunar line,"[8] etc.) is a ventral hernia occurring near the lateral border of the rectus muscle, in or near the musculoaponeurotic structure known as the semilunar or Spigelian line. This line is, in fact, a rather broad musculoaponeurotic band, extending from the 8th and 9th costal cartilage to the pubic tubercle, lateral to the rectus muscle and constituted by the fusion of the transversus aponeurosis with the posterior leaf of the internal oblique aponeurosis (Spigelian Fascia).[1] This fascia is strong, but has nevertheless some weak areas, such as the hiatuses through which the lateral branches of the deep epigastric artery pass,[2,3,20] irregular slit-like defects lateral to the rectus border[21] and gaps created by the banding of the internal oblique and transverse muscle fibers.[23] These several types of defects may become superimposed, since in their caudad half the muscle fibers of the internal oblique and transverse run parallel.[9,15] Recently it has been suggested by Olson and Davis[17] that previous abdominal incisions may play a role in the etiology of Spigelian hernia. In two of their six cases and in five of our own there had been previous abdominal operations. In addition we found in the literature 51 cases with pertinent anamnestic data, in 32 of which there was a history of previous abdominal operations. This makes a total of 66 patients with available histories, 39 with abdominal wall scars. The lack of data in the remaining cases precludes of course valid statistical analysis, but the proportion of more than 50% remains highly suggestive. It is possible that the contraction of a scar in the vicinity of a weak area in the semilunar fascia may weaken it even further.

A Spigelian hernia can occur theoretically anywhere along the semilunar line. However, the vast majority occur at or near the level of the semicircular (Douglas') line. Since the precise location of this line varies,[14] so does the site of the hernial orifice, which may be found from the

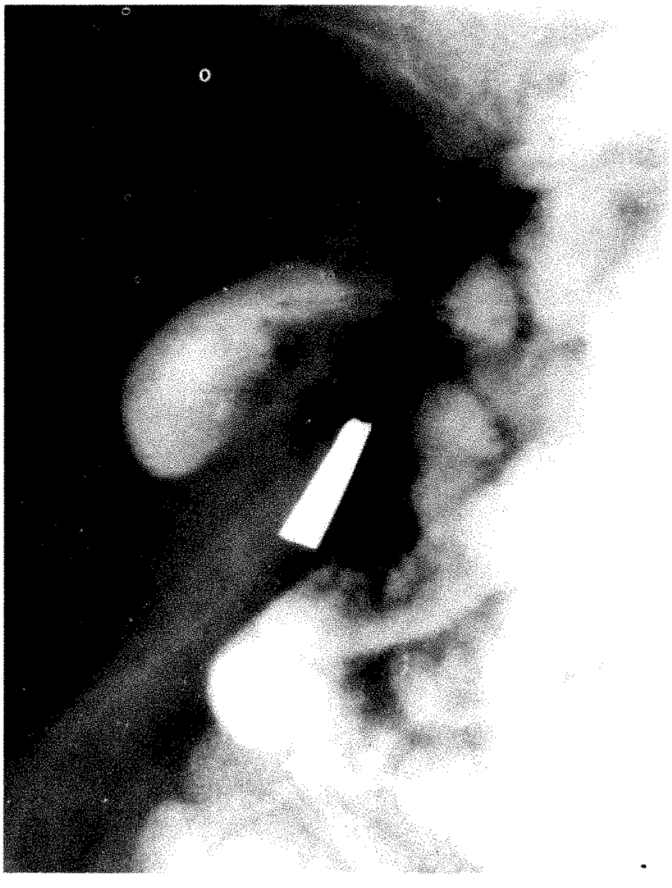
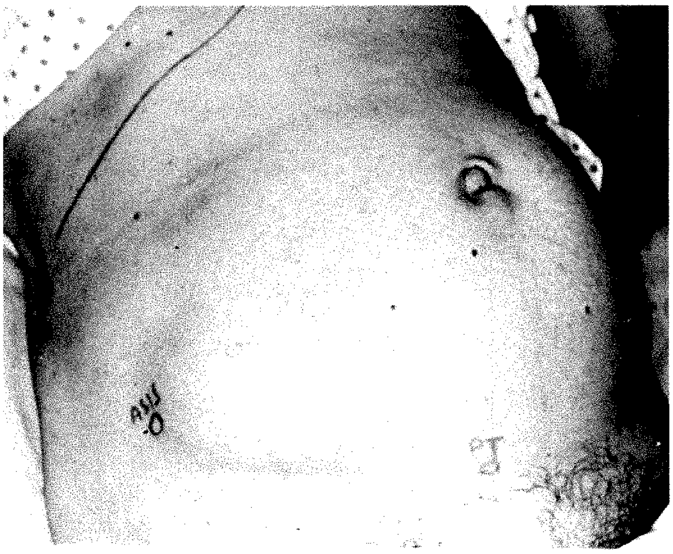


FIG. 2. Case 3. Oblique projection, opaque marker indicates centre of mass.



IG. 3. Case 5. Markings show costal margin, anterosuperior iliac spine nd public tubercle. The small circle medial to the iliac spine marks the entre of the hernia.

evel of the umbilicus to the inguinal area. On rare ocasions the mass *and* the hernial orifice are situated ephalad to the umbilicus.[10,11,13,22]

ncidence

From the literature available to us, 295 cases have been oted and of those 178 had pertinent anamnestic data. The rue incidence is probably greater; a number of patients nay not have been considered worth reporting or the leion may not have been recognised.

The age of onset varies widely and Spigelian hernias ave been described also in children. The peak incidence ccurs in the 4th, 5th and 7th decades. Both sexes are qually affected. Cumulative data from case reports show a nale to female ratio of 1/1.05. The right side is twice as requently affected. There are four reported instances of ilateral Spigelian hernia.[4,7,19] Of 178 cases 43 were inarcerated and of these 25 strangulated.

iagnosis

Spigelian hernias are masked by the abdominal fat and he aponeurosis of the external oblique and thus easily lude detection. A history of sudden or sustained physical ffort, chronic straining, obesity and previous abdominal perations are often noted. The most frequent symptom is ain. It was reported in 119 of 178 patients and was present in all our cases. It is usually localized at the hernial ite and straining of the abdominal musculature frequently ncreases the pain.

The next most frequent sign is the presence of a lump. It vas noted by the patient in 97 cases and by the physician n 14. Each of our nine cases presented with a mass. nother important physical sign is localized tenderness. It vas elicited in six of our patients. Sometimes it may be the only sign and in some cases the diagnosis was made and surgery undertaken on its strength alone.[5]

The diagnosis of Spigelian hernia depends to a great extent on awareness of its possible occurrence. The history of pain and the finding of a lump adjacent to the rectus border should lead to the correct diagnosis. However the associated symptoms frequently tend to obscure the diagnosis due to their vague and misleading character. The correct preoperative diagnosis was made in only 92 cases out of 178, while the remainder were diagnosed as appendicitis, postoperative adhesions, abdominal tumors, intestinal obstruction, etc. Several patients were subjected to exploratory laparotomies and others underwent lengthy diagnostic procedures. It is significant that in our cases the last six were detected during the past 18 months and correctly diagnosed preoperatively.

Treatment

The treatment of Spigelian hernia is surgical and follows the usual principles of hernia repair; excision of the sac and repair of the wall. The incision (preferably transverse) is centered on the mass and carried down to the external oblique aponeurosis which is split in the direction of the fibers. The sac is dissected free down to the hernial orifice (Fig. 4) and is excised; the peritoneum is closed by a purse-string or interrupted sutures. The repair is carried out by closing the muscles in layers using non-absorbable interrupted sutures and imbricating the external oblique aponeurosis in the Mayo fashion.

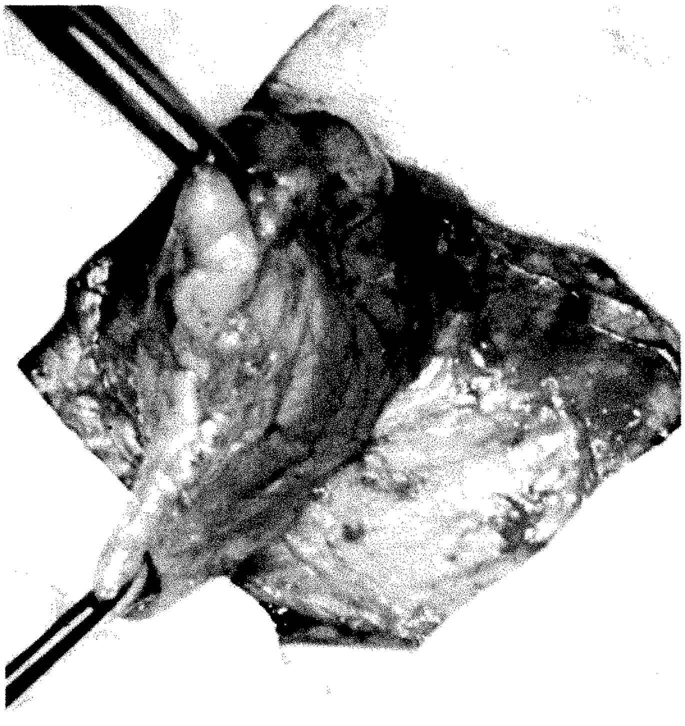


FIG. 4. Case 5. The aponeurosis of the external oblique has been split, the sac dissected free from the surrounding tissues and pulled upwards to expose the neck which is protruding through the fibers of the internal oblique.

There are only three instances of recurrence reported in the literature[12,16,17] and of all the operated patients only two died of postoperative complications.[5,18] Our cases have been followed for periods of six months to five years and no recurrences were noted.

Addendum

Since the completion of this manuscript an additional case of Spigelian hernia was discovered. The patient was a 28-year-old factory worker, with a five-year history of intermittent right lower quadrant pain. There was no swelling and no previous abdominal surgery. Due to the awareness of our staff the patient was admitted with the diagnosis of Spigelian hernia. On examination there was marked tenderness at the lateral rectus border, at the level of the iliac spine. A soft mass 3 cm in diameter was palpated at this point. At operation a Spigelian hernia was found. The sac measured 3 × 3 cm and contained the caecum and the appendix. The appendix was removed and the abdominal wall repaired in the usual manner. The patient made an uneventful recovery.

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Analysis of Injury in Complex Organ Preservation

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A biochemical assay of renal viability previously described for rabbits is validated in a canine model using anoxia, hypothermia, and hypothermic perfusion. The assay correlated well with the decree of anoxic injury and protective effect of hypothermia. It was found to be unable to document significant injury when pulsatile perfusion was added to the system and resulted in nonviable canine kidneys. Apparent vascular damage with interstitial hemorrhage occurred after the perfusion and was not predictable by the use of the assay system. The limitations of any assay for organ viability after complex preservation maneuvers is the result of a multiplicity of injurious factors surrounding the preservation or as a consequence of the preservation. No single assay system will be adequate for protection of organ viability during or after preservation as long as the types of injury are multiple. Is is suggested that great care be used in defining possible injurious factors associated with given preservation maneuver and that specific assays be utilized to document the effects of each of these factors. The more complex the preservation system employed; the more complex the assay system needed.

ORGAN INJURY associated with preservation maneuvers has been definitely correlated with anoxia and hypothermia, but there may be other factors, as yet undescribed, limiting the duration of preservation, particularly perfusion preservation. Methods of assaying viability (or in another sense, absence of injury) are many, but often nonspecific and inaccurate. A complex biochemical system of *in vitro* analysis has been described[2] and has been useful in identifying preservation injury in a quantitative fashion and has been directly related to functional survival of whole organs.

In this study, a different animal species has been used to validate this system of viability assay and to attempt to identify modalities of injury in addition to anoxia and hypothermia. Standard perfusion techniques have been employed to approximate clinical organ preservation.

Methods

Techniques of In Vitro Analysis

The basic techniques for *in vitro* analysis have already been described.[2] Briefly, however, slices of dog renal cortex of 0.4–0.5 mm thickness are prepared in Stadie-Riggs microtome and placed in Warburg flasks containing a small volume of a chilled artificial extracellular fluid medium at a pH of 7.4 calculated from Sorensen Tables. The osmolality of this medium, as determined by freezing point depression, was 290–300 mOsm. All work was performed at 5 C except where otherwise specified.

The center well of the Warburg flasks contained 0.2 mm of 20% potassium hydroxide and two thermobarometers were always utilized to give maximum manometric control. The flasks were incubated for 30 minutes in the presence of 100% oxygen at 37 C. Oxygen consumption (QO_2) was then measured for another 30 minutes, the slices and medium were separated, and the slices weighed.

The medium was analyzed for glutamic oxaloacetic transaminase (GOT), glutamatic pyruvic transaminase (GPT), lactic dehydrogenase (LDH), beta-glucuronidase (B-glu), lactate, acid phosphatase (acid phos), and alkaline phosphatase (alk phos). All values were corrected to tissue weight.

The media was individually centrifuged at high velocity, transferred into freezing vials, and placed into liquid nitrogen. Liquid nitrogen storage was found necessary to preserve maximally the small quantities of enzyme

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The opinions or assertions contained herein are the private ones of the authors and are not be be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

The experiments reported herein were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care."

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released by the small tissue slices. Preliminary experiments with varying storage times showed that there was no loss of any enzyme activity as long as liquid nitrogen was employed and no longer than five days of storage before determinations were made.

Calculations

The values obtained from 25 normal kidneys were used as the control determinations. For ease of expression, the results from the experimental kidney slices were compared to those of the control kidney slices as ratio called the In Vitro Factor (IVF). In all cases the experimental value was divided by the control value with the exception of oxygen consumption which is expressed as the reciprocal for uniformity.

$$\frac{\text{Experimental Value}}{\text{Control Value}} = \text{In Vitro Factor}$$

Experience in other species have shown that this is a general trend and that all factors with the exception of oxygen consumption do, in fact, rise so that the inversion of the oxygen consumption figure is a valid maneuver to assure uniformity.

Overall injury was then expressed as a composite expression, the average, formed by the simple addition and division of all of the In Vitro Factors to make an In Vitro Index.

$$\frac{\text{IVF}_1 + \text{IFV}_2 + \cdots \text{IVF}_n}{n} = \text{IVI}$$

The variation of oxygen consumption from animal to animal was so great under the experimental conditions that the oxygen consumption of the contralateral kidney at the time of the experimental procedure was used as the control value.

If both the experimental kidney and its control values were normal, then the results theoretically being the same should lead to In Vitro Factors of 1.0 and the average of the eight factors would then give an In Vitro Index of 1.0. Variations upward from 1.0 could be interpreted as denoting increased damage and downward deviations as lessened damage and/or protection. For the index to be less than 1.0 would be possible only in experiments where the control was not "normal," as will be seen below. We feel that this is quite possible since any manipulation will cause some damage no matter how slight and that the control kidneys are not toally free from injury.

Experimental Groups

All experiments involve the use of mongrel dogs, of either sex, weighing 25–35 kg with ten animals in each group. All procedures were carried out under a combination Nembutal-nitrous oxide/oxygen anesthesia with the animals fully intubated with assisted respiration. The kidneys were approached through a midline incision with a direct skeletonizing of the kidney and its vasculature. All nervous connection with the kidney was carefully eliminated. Both ureters were catheterized and tourniquet sutures placed around the ureters to avoid back flow via the ureteral vasculature.

The control (contralateral) kidneys were than quickly excised after rapid ligation of the renal artery and veins and quickly transferred for the *in vitro* analysis. The total of warm ischemia for these control kidneys was always less than five minutes. Kidneys for control determinations were taken from a total of 25 animals, including the contralateral kidneys of the experimental animals.

Following the removal of the control kidney, the animal then underwent either a perfusion or an anoxia study described below under experimental groups I through VI. Following the experimental procedures the experimental kidney was carefully retroperitonealized and the midline incision closed. The animals were returned to their cages with antibiotic coverage and food and water *ad lib.*

Experimental Group I: 60 Minute In Situ Renal Anoxia, 37 C

In this group of animals, following the removal of the contralateral kidney for control determinations, the animals were given aqueous heparin, 2 mg/kg intravenously. A period of five minutes was allowed to elapse and then the blood supply to and from the experimental kidney was occluded with atraumatic clamps. Thermister probes for measurement of renal temperature were inserted into experimental renal medulla and cortex. The bowel was replaced into the abdominal cavity and a period of 60 minutes allowed to elapse.

Following the experimental period, a renal biopsy was taken for the *in vitro* analysis and the blood flow to the kidney re-established by removing the atraumatic clamps. The kidney was retro-peritonealized, the abdominal incision closed, and the animal returned to its cage with antibiotics and food and water *ad lib.*

Experimental Group II: 90 Minutes In Situ Renal Anoxia 37 C

This group is exactly the same as Experimental Group I with the exception that the warm ischemia time was 90 minutes instead of 60 minutes. All other aspects of the experiment and the subsequent treatment of the animals was the same.

Experimental Group III: 120 Minutes In Situ Renal Anoxia 37 C

This group is exactly the same as Experimental Group I with exception that the warm ischemia time was 120 minutes instead of 60 minutes. All other aspects of the experiment and the subsequent treatment of the animals was the same.

Experimental Group IV: 60 Minute Normothermic (37 C) In Situ Renal Perfusion

Following removal of the control kidney, skeletonization of the experimental kidney, and systemic heparinization, catheters were carefully placed in the renal artery, renal vein and ureter. Catheter size selection was always made to be equal to or slightly greater than the lumen of the experimental kidney's artery or vein. Catheters were placed in the renal artery and vein of the experimental kidney via the stumps of the control kidney, renal artery, and vein.

A renal vein hydrostatic pressure of approximately 6 cm of water was applied to the experimental kidney and perfusion was carried out as described below. The temperature of the kidney was kept 36–37 C as measured by surface and deep core thermister probes.

Following the 60 minutes of perfusion, the flow was stopped, renal biopsy taken for the *in vitro* analysis, and blood flow to the experimental kidney re-established by removing the catheters from the orifices of the renal artery and vein. The stumps of the contralateral renal artery and vein were secured, the experimental kidney retroperitonealized and all other aspects of the experiment being essentially the same as the other groups.

Experimental Group V: 60 Minute Hypothermic, (10 C) In Situ Renal Perfusion

This group is the same as Experimental Group IV with the exception that the core temperatures of the kidneys were 8–11 C.

Experimental Group VI: 300 Minute Hypothermic (10 C) In Situ Renal Perfusion

This group is the same as Experimental Group V except for the extended time of perfusion of 300 minutes.

Perfusate and Perfusion Dynamics

The perfusion was carried out by a pediatric-type pulsatile pump of the bileaflet valve variety and with a membrane oxygenator and a coil heat exchanger made by the Waters Company. The source of gas for the membrane oxygenator was 95% air, 5% CO_2 with CO_2 added, if necessary, to keept the range of arterial PCO_8 between 30 and 40 mm Hg. The PO_2 was allowed to equilibrate spontaneously and the arterial PO_2's for the 37 C perfusion ranged 130–140 mm Hg. In the hypothermic perfusion the values of the PO_2 ranged 180–190 mm Hg. A systolic pressure of 65–70 mm Hg with a diastolic of 45–50 mm Hg was set and maintained for all experiments with the flow being dependent upon the pressure.

Filters were placed in the line just proximal to the arterial inlet and pressure and flows were measured periodically. The perfusate consisted of 2% low-molecular weight dextran in Hank's-balance salt solution with the addition of hydrocortisone acetate 100 mg/100 ml.

Gravity flow for urine was provided to prevent increased renal pelvic pressure.

The pH was maintained with the range of 7.35–7.45 by CO_2 adjustment and bicarbonate addition.

Results

Experimental Group I: 60 Minute In Situ Anoxia, 37 C

Following the anoxic period, the kidneys were restored to the circulation with rapid filling and restoration of the normal turgor. Kidney color appeared to be normal and many of the kidneys started to produce urine within seconds of the re-establishment of circulation. There was no evidence of abnormal bleeding and renal biopsies produced bright red bleeding, indicating peripheral (cortical) oxygenation and perfusion.

Chemical analysis, that is, the *in vitro* analysis, is demonstrated in Table 1.

All parameters measured with the exception of GOT and alkaline phosphatase had no or minimal change as indicated by an In Vitro Factor of approximately 1.0. The overall average indicator of cell damage, the In Vitro Index, was 1.2 indicating that some cellular damage over and above the control level occurred. The initial rapid rise in GOT and alkaline phosphatase in response to 60 minutes of anoxia corresponds quite well with the sensitivity of the same enzymes in the rabbit system as described by Abbott and Sell.[2] Unlike the rabbit system, acid phosphatase does not appear to be as sensitive an indicator of anoxic damage in the dog.

Correlation of the *in vitro* analysis (the chemical results), with the clinical progress of the animals indicated that this amount of damage (IVI equalled 1.20) is certainly compatible with life and probably represents a completely reversible cellular insult. All animals in this group lived for 30 days postoperatively with only a minimal BUN rise (plus 20 mg. %) during the first three postoperative days and then return to the preoperative levels by the fifth day. At the end of the 30-day holding period all creatinines were completely normal with active healthy animals.

TABLE 1. *60-Minute in Situ Renal Anoxia*

	QO_2	GOT	GPT	LDH	Alk. Phos.	Acid Phos.	Lact.	B-GLU
Normal	195	165	48	1668	42	13	9	13
Experimental	165	227	50	1986	66	12	11	14
In Vitro Factor	1.18	1.37	1.04	1.19	1.57	0.95	1.17	1.11

In Vitro Index = 1.20

Experimental Group II: 90 Minutes In Situ Renal Anoxia, 37 C

In this group of animals the results during and following the operative procedures were considerably different than from Group I. Following the anoxic period the restoration of the circulation resulted in one of two patterns. The first pattern was that a rapid restoration of cortical flow with bright red bleeding for one or two minutes and then rapid progressive ischemia of the cortical areas. This was accompanied by a decrease in kidney turgor and no urine was produced. The second pattern was simply a lack of turgor initially with poor cortical perfusion. Bright red blood can only be found when the renal biopsy was carried well into the deep medulla. Again no urine was produced. There was no evidence of thrombosis in either the renal artery or renal vein. The *in vitro* analysis can be seen in Table 2.

The overall impression is a continued increase in the In Vitro Factors indicating a continued damage to the cellular systems. One blatant exception to this pattern is alkaline phosphatase which has dropped from a value of 1.57 at the end of 60 minutes to an In Vitro Factor of 1.02 for 90 minutes of anoxia. This change is inexplicable at the present but is commonly seen in this type of experimentation. The rabbit system describes an identical drop in the alkaline phosphatase at 120 minutes of anoxia. The significance of this drop is not readily apparent.

Oxygen consumption and lactate production are represented by a significant increase in the In Vitro Factor, probably indicating that anaerobic metabolism has taken predominance in the system at this point. Lactate dehydrogenase does not appear to change much between 60 and 90 minutes of anoxia and this is consistent with the results obtained in rabbits where there is very little change in LDH between 60 and 120 minutes of anoxia. The overall view in terms of the In Vitro Index indicates that there is an additional insult to the kidney in its overall metabolism represented by the In Vitro Index No. 1.32.

This increase in the In Vitro Index correlates with the clinical results. Eighty per cent of the animals in the group failed to survive seven postoperative days. The remaining 20% lived for the 30-day holding time postoperatively and at the end of that period had a normal serum creatinine and BUN level. The animals that died within the first seven days had a rapid rise in their BUN and creatinine and no urine output.

Autopsy of the dead animals revealed a shrunken kidney in the process of partial necrosis with patent artery and veins. Sacrifice of the survivors at the end of the 30-day period revealed a normal appearing kidney with no areas of infarction or necrosis.

Experimental Group IV: 120 Minutes In Situ Renal Anoxia, 37 C

In this group of anoxic animals the results during the operative procedure were identical with Group II. The *in vitro* analysis can be seen in Table 3.

The overall damage as indicated by the rise in the In Vitro Factors is distributed throughout the parameter's measure. GOT and alkaline phosphatase continued to be the most sensitive indicators of anoxic damage in the dog but at 120 minutes of renal anoxia, LDH and GPT have increased considerably also, as an overall indication of injury. It is of significance that this secondary rise in all factors is comparable to the rabbit material previously described.

The rapid increase in the In Vitro Index (1.53) correlates very well with the clinical material. None of the animals in this group survived. All animals had expired by the fourth through the sixth day with BUN's and creatinines running as high as 200 mg % and 13 mg % respectively. None of the animals produced any significant amount of urine and the majority of the animals produced no urine at all postoperatively.

Autopsy of these animals revealed a shrunken partly necrotic kidney with patent artery and vein.

Experimental Group IV: 60-Minute Normothermic In Situ Renal Perfusion

The perfusion dynamics for this 60-minute period were satisfactory with an intial flow of 1.09 cc/gm/min and at the end of the 60-minute period a final flow of 1.81 cc/gm/min. The A-V difference of PO_2 was approximately 83–90 mm Hg, resulting in an oxygen consumption of 0.12–0.217 μm/gm/min. The normal oxygen consumption

TABLE 2. *90-Minute In Situ Renal Anoxia*

	QO_2	GOT	GPT	LDH	Alk. Phos.	Acid Phos.	Lact.	B-GLU
Normal	206	165	48	1668	42	13	9	13
Experimental	153	262	55	1804	43	20	15	15
In Vitro Factor	1.35	1.58	1.14	1.08	1.02	1.51	1.71	1.18

In Vitro Index = 1.32

TABLE 3. *120 Minutes In Situ Renal Anoxia*

	QO_2	GOT	GPT	LDH	Alk. Phos.	Acid Phos.	Lact.	B-GLU
Normal	247	165	49	1668	42	13	9	13
Experimental	186	250	84	2915	87	17	12	16
In Vitro Factor	1.33	1.52	1.74	1.75	2.06	1.31	1.36	1.20

In Vitro Index = 1.53

TABLE 4. *60-Minute Normothermic (37 C) In Situ Renal Perfusion*

	QO_2	GOT	GPT	LDH	Alk. Phos.	Acid. Phos.	Lact.	B-GLU
Normal	205	165	48	1668	42	13	9	13
Experimental	161	180	94	2085	92	29	11	21
In Vitro Factor	1.26	1.09	1.96	1.25	2.19	2.20	1.22	1.63

In Vitro Index = 1.60

for a dog kidney at normothermic temperature is 3.0–5.0 μm of oxygen/gm/min.[3]

Following restoration of normal circulation, the kidneys immediately blushed and then tended to become somewhat dusky with poor turgor and no urine formation. Biopsy resulted in bright red bleeding only when the deep medulla was entered. Table 4 shows the *in vitro* analysis for this period of hypoxic renal perfusion.

The overall indication of damage, that is, the In Vitro Index was higher than in the 60-minute anoxic period. The value of 1.60 represents considerable cellular damage. However, the distribution of the indicators and the rise in the indicators is considerably different in the perfusion group than in the renal anoxia group. GOT which had been a sensitive indicator of anoxic damage is relatively unchanged in the perfusion model. GPT, however, is considerably higher in the 60-minute perfusion than in the 60-minute anoxia and is comparable to the 120-minute renal anoxia figure. Alkaline phosphatase again is a consistent and sensitive indicator to renal insult as indicated by the In Vitro Factor of 2.19. Factors which were changed only minimally in other situations appeared to be considerably elevated in the perfusion model, primarily acid phosphatase and beta-glucuronidase with In Vitro Factors of 2.20 and 1.63 respectively.

The elevated In Vitro Index of 1.60 corresponds well with the clinical progress of the animals in this group. All animals died before the seventh postoperative day with BUN and creatinine elevations of 250 mg % and 12.5 mg % respectively. None of the animals produced urine and upon autopsy revealed shrunken necrotic kidneys with an intact hilar vasculature. There was no evidence at any time of renal artery or venous thrombosis.

Experimental Group V: 60-Minute Hypothermic (10 C) In Situ Renal Perfusion

The perfusion data for the hypothermic renal perfusion was extremely constant. The core temperature and cortical temperatures ranged 8–11 C throughout the experimentation and renal artery pressure was constant at 70 mm Hg systolic and 45 mm Hg diastolic. Flow through the renal artery ranged between 0.834 cc/gm/min at the onset to 0.984 cc/gm/min at the end of the 60-minute interval. This resulted in an oxygen consumption of 0.13–0.16 μm/gm/min for the perfusion period, which is quite comparable to the normothermic values.

However, upon restoration of the circulation, all kidneys immediately blushed and retained their cortical perfusion throughout the operative examination. In the majority of cases urine was produced within seconds, and in all cases within minutes or restoration of circulatory flow. The biopsy revealed bright red blood from the cortex indicating peripheral perfusion. Chemical analysis (In Vitro Analysis) can be seen in Table 5.

It is quite clear that our indicator of damage, the In Vitro Index is considerably below the control value. This drop in the In Vitro Index below control levels is not unexpected. As the controls were described it can certainly be seen how some anoxic or manipulative damage could occur to the kidneys as they go through the control procedure. The hypothermic perfusion may in fact protect the kidneys to a much greater extent than one may anticipate and in fact improve the values below that seen in the control model.

It is of interest, however, that the In Vitro Factor for lactate is still elevated at 1.36 indicating that despite what is considered to be a significant amount of protection, there has been some anaerobic metabolism producing an elevated lactate. Our two original sensitive indicators of anoxic damage SGOT and alkaline phosphatase are considerably lower than the rest of the values with the exception of acid phosphatase. This may substantiate the supposition that the control values doe have a considerable anoxic damage going on during their manipulative procedure and that the rapid installation of hypothermia would protect against this type of damage.

The clinical course of the animals correlates extremely well with the In Vitro Index. All of the animals survived the 30-day postoperative period with minimal elevation of the BUN and creatinine. All values for BUN and creatinine

TABLE 5. *60-Minute Hypothermic (10 C) In Situ Renal Perfusion*

	QO_2	GOT	GPT	LDH	Alk. Phos.	Acid Phos.	Lact.	B-GLU
Normal	178	165	48	1668	42	13	9	13
Experimental	162	111	44	1290	25	7	12	9
In Vitro Factor	1.10	0.67	0.92	0.77	0.59	0.54	1.36	0.65

In Vitro Index = 0.83

were normal by the fifth postoperative day and remained normal throughout the 30-day postoperative period. All animals were healthy and active demonstrating no residual of their operative procedure.

Experimental Group VI: 300-Minute Hypothermic (10 C) In Situ Renal Perfusion

Following the completion of the perfusion the vascular continuity to the kidney was re-established and the results were as follows:

Immediately after restoration of the circulation the kidney immediately blushed and became quite tense. There was no evidence of obstruction to outflow but the renal vein did not demonstrate much flow. No urine was produced. The kidney became quite cyanotic and remained tense and demonstrated minimal bleeding when a biopsy was taken. *In Vitro* Index is shown in Table 6.

The overall pattern of injury as demonstrated by the In Vitro Index is one of minimal or no injury at all. An In Vitro Index of 0.88 indicates that little parenchymal damage has occurred. The majority of the individual factors, especially lactate and GPT, are reduced considerably below the "normal" value of 1.0. The In Vitro Factor for oxygen consumption, however, does seem to be somewhat elevated and may be the only forecast of the clinical course.

The chemical analysis as it is constructed presently does not correlate well with the clinical course of these animals. All animals died within five days of the procedure with extremely high BUN's and serum creatinines. The course was typically a renal failure with uremia. At autopsy the kidneys appeared somewhat larger than usual, very tense despite the lack of perfusion. The main renal vasculature was intact and showed no evidence of obtruction or thrombosis either on the arterial or venous side. However, sectioning of the kidney revealed massive intrarenal hemorrhage, particularly in the area of the medulla. Microscopic section confirmed the interstitial hemorrhage with disruption of the intima of the smaller arterioles. No urine was found in either the renal pelvis or the bladder.

Discussion

This experimental model demonstrates that the *in vitro* analysis has definite value in predicting and quantifying anoxic damage to canine kidneys. The overall results in the dogs favorably approaches the rabbit studies of Abbott and Sell. Although the parameters measured cannot be individually depended upon to predict cellular damage, the overall pattern and the average of the whole group is consistent in its increasing value with increasing damage secondary to anoxia. This reliability of the *in vitro* index is especially helpful in the laboratory for manipulations which are super-lethal. Without this type of quantitative analysis, no difference can be noted between various maneuvers, all of which result in nonfunction. For instance, in this study, 120 minutes and 90 minutes of anoxia led to nonfunction of the kidneys. However, 120 minutes of anoxia creates more cellular damage as evidenced by a higher *in vitro* index than the 90 minutes of anoxia. The direction indicated, namely selecting less anoxia leads to function in a corresponding lower *in vitro* index. Although this type of laboratory analysis is cumbersome and time consuming, it is reliable and is exactly the type of analysis needed for a variety of preservation manipulations, especially freezing experiments.[1]

More investigation is needed to select parameters which will give greater consistency in their direction of change with a specific injury. Ideally these parameters would be easier to obtain than those chosen for this study. Nonetheless, it is more than likely that a set of parameters rather than a single test will be necessary to diagnose and quantitate renal injury under preservation circumstances.[4]

The results of this study also point out that any given set of parameters may only reflect damage in certain compartments of the organ undergoing manipulation. The *in vitro* index as constructed for this group of experiments appears to be reasonably reliable in dealing with cellular injury from anoxia. However, it does not appear to be reliable in predicting damage done to other compartments of the organ. This is evidenced by the suggestion that the cellular environment of the 300-minute perfused kidneys under hypothermic conditions was adequately preserved with an *in vitro* index of less than one. Nonetheless, all of the organs failed to function and showed histologically extra-cellular hemorrhage and disruption of small arterioles. Obviously, the *in vitro* index as presently constructed gave no indication that damage was being done to compartments of the kidney outside the parenchymal cells. It is quite possible enzymes or substrates unique to the cells of the vascular system might be monitored in a similar fashion and be used to herald another type of injury.

The results of this group of experiments suggests and reinforces the concept that renal damage is being created

TABLE 6. *300-minute Hypothermil (10 L) In Situ Renal Perfusion*

	QO_2	GOT	GPT	LDH	Alk. Phos.	Acid. Phos.	Lact.	B-GLU
Normal	195	165	48	1668	42	13	9	13
Experimental	118	184	29	1232	32	9	2.24	16
In Vitro Factor	1.65	1.11	0.60	0.74	0.76	0.69	0.25	1.23

In Vitro Index = 0.88

even under controlled experimental conditions by the mere manipulation of the kidneys. Certainly the kidneys which were hypothermically perfused with a minimal amount of manipulation had lower values for most of the parameters than did the "normal" kidneys which were subjected to surgical dissection and removal. This suggestive damage may be transient in nature, but the need for preoperative protection is reinforced.

In summary, this group of experiments substantiates the work of Abbott and Sell and proves a useful tool in studying renal preservation and renal injury in the dog. In addition, it is suggested that any given system of analysis may not be applicable to all types of injury no matter how reliable it is with one specific type of injury. Renal preservation maneuvers may in themselves be injurious in an unsuspected fashion while at the same time decreasing or preventing the damage in another fashion. Clearly, for long term preservation and certainly for more predictable short term preservation, it would be useful to clearly delineate the various injurious factors and the compartment within the organ system where they have an effect.

The described system of viability analysis has proven useful in several animal systems and is predictable at least where the injurious effects of anoxia and hypothermia are concerned. More specific and predictable *in vitro* factor selection will increase the ability of this system to quantitate injury due to these factors. However, all systems of viability analysis should not only predict damage and quantitate it; but should also clearly identify the modalities of injury represented by the analytic system. Great caution should be exerted when attempting to correlate viability assays with complex systems of preservation. A cautious and critical outlook regarding such results should prevent over-enthusiasm for some specific preservation maneuver. On the other hand, potentially valuable preservation maneuvers might be lost in the disappointment of organ failure. The realization that an individual compartment may have been benefitted by the maneuver and the need to retain that particular maneuver in the total system of preservation should help to advance the art and science of organ preservation to a more perfect state.

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Long Term Evaluation of Omental Transposition for Chronic Lymphedema

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A series of patients treated with omental transposition for chronic lymphedema of an extremity is presented. Several surgical steps in the procedure are stressed and the results and complications of the operation listed. The major drawback of the procedure is that the peritoneal cavity must be entered. Success following omental transposition can be expected in approximately one-third to one-half of patients.

A REPORT published in 1966 described the use of the intact omentum for treating patients with chronic lymphedema of an extremity.[4] Transposition of the omentum for this condition was based on the hypothesis that discontinuity of lymphatic and lymphovenous systems within the lymphedematous extremity would be bridged by lymphatic and vascular structures in the omentum.

The purpose of this paper is to report the long-term results of omental transposition and changes in surgical technique that have evolved from continuing experience with the operation.

Surgical Technique

Early reports on omental transposition showed that the structure could be lengthened to the elbow or knee by simply dividing omental attachments to the transverse colon and from a major portion of the greater curvature of the stomach.[3] Further anatomical and surgical experience with the omentum now allows the structure to be elongated to practically any area of the body by dividing it in relation to its vascular architecture (Fig. 1).[1] Several technical steps in the operation have been altered over the years. These changes and several other points in the procedure are listed below.

1. A midline incision is adequate for elongating the omentum; an upper incision for the arm and a mid to lower incision for the leg.
2. The anterior layer of the gastrocolic omentum is occasionally fused to the transverse mesocolon. When it is necessary to separate these two structures, care must be taken to prevent damage to the middle colic vessels within the transverse mesocolon.
3. When the omentum is freed from attachments in the left upper quadrant, it is advisable to place two clamps on any sizable blood vessel in the area, since slippage of a single clamp or the loosening of a knot below a single clamp during the process of tying, can result in the retraction of a bleeding vessel high into the left upper quadrant. This occurred once to the author early in the series and is an event well remembered.
4. The surgical technique used in early cases of omental transposition to the leg allowed for the omentum to be brought out of the peritoneal cavity through a small retroperitoneal opening overlying the iliac vessels. From this opening, a tunnel was created anterior to the femoral vessels, which required division of the inguinal ligament. The omentum was carried through this tunnel and subsequently draped as an omental apron over the underlying muscles of the leg. This technique has been changed to that used for omental transposition to the arm whereby the omentum is simply brought out of the abdominal cavity at the end of the abdominal incision and placed subcutaneous into the involved limb. This simplifies the operation and eliminates the chance of developing an inguinal hernia.
5. That part of the lengthened omentum which remains within the abdominal cavity must be secured so as to minimize the chance of developing an internal hernia. It is important to remember when fixing the intraperitoneal portion of the omental pedicle that the needle not impinge upon the artery or vein in the omental pedicle since it is these vessels which supply and drain the vascular system of the lengthened omentum.
6. All suture material used in a lymphedematous ex-

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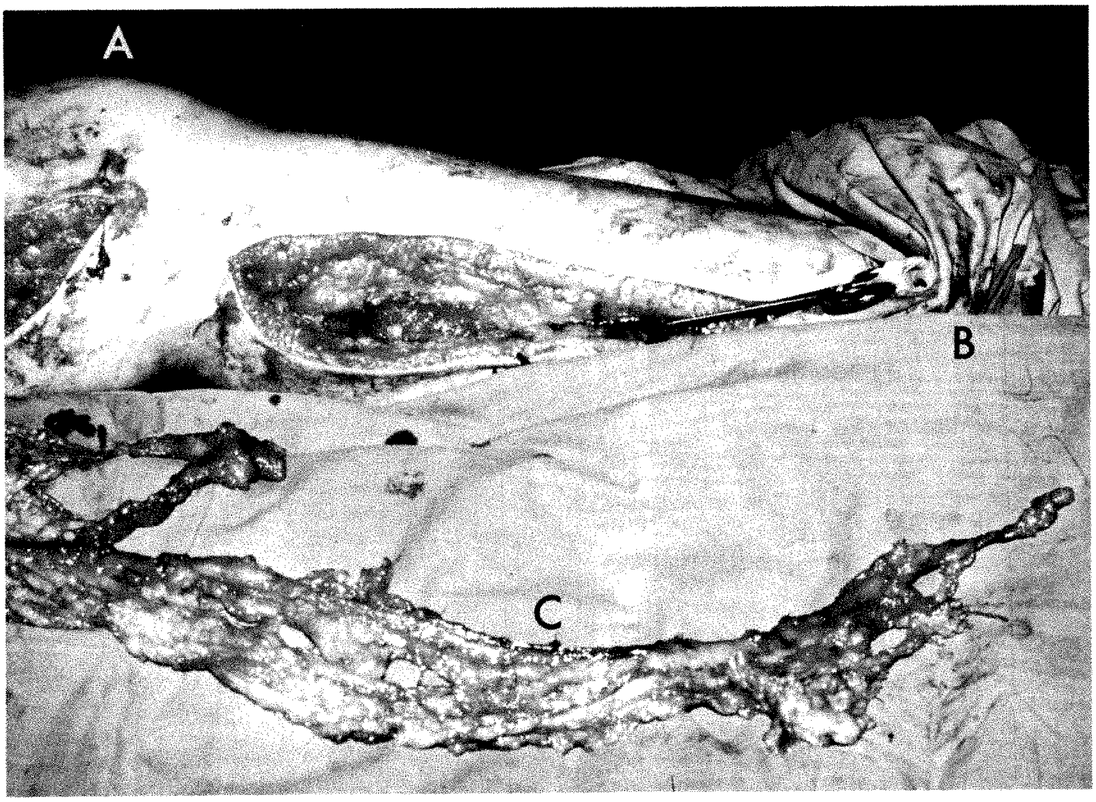

Fig. 1. Pedicled omentum prior to being placed in median tunnels along thigh and lower leg (A. knee, B. ankle, C. intact omentum).

tremity should be absorbable except for the skin sutures. If non-absorbable sutures are used and a wound infection occurs, the continued presence of the foreign material in lymph fluid can lead to a persistent problem.

7. All incisions in a lymphedematous extremity must be closed with great care, for if the wound separates, regardless of how small the separation, lymph fluid can drain through the opening for a long period. To obviate this potential problem, multiple small sutures are used to approximate both the subcutaneous and cutaneous layers of the skin. Skin sutures are usually left in place for a longer period of time than is customary with other types of operations.

Results

There were 22 patients in this series; 13 with lymphedema of the leg and 9 of the arm. Only patients who have had a followup period of at least one year were included in this series. The longest followup period is over seven years.

Results of the operation are based on objective criteria listed in Table 1. A clinical result was considered good if at least one of the criteria listed in Table 1 occurred in addition to the patient's favorable evaluation of his postoperative response. If one or more criterion listed in Table 1 occurred, but the patient did not believe that his operation had been worthwhile, the result of the procedure was listed as poor. Table 2 shows the operative results.

Complications of omental transposition are listed in Table 3. The patient (C.G.) with upper intestinal obstruction and patient (R.W.) who had a pulmonary embolus and a stress ulcer, developed their complications shortly after being discharged from the hospital. C.G. not only had a severe complication, but was doubly unfortunate in that she had no response to omental transposition. The patient (R.W.) who is now more than seven years after omental transposition, has continued to consider her operation worthwhile in spite of its complications.

The most devastating long-range postoperative complication was in a teenage male who, three and one-half years after surgery, considered the results of his operation to be excellent; an evaluation shared by his family and this

Table 1. *Objective Criteria*

1. Diminution in size of involved extremity.
2. Diminution or disappearance of attacks of lymphangitis and cellulitis of lymphedematous limb.
3. Increased function of the involved extremity.
4. Marked decrease in the tissue turgor of the lymphedematous limb.

Table 2. *Operative Results: Omental Transposition*

Leg		Arm
(1-7 year followup)		(3-7 year followup)
13 Patients		9 Patients
Results	Good—5 (38%)	Good —5 (56%)
	Fair—3 (23%)	Fair—1 (11%)
	Poor—5 (38%)	Poor—3 (33%)

TABLE 3. *Complications*

Omentum to Leg	Omentum to Arm
M.J.—Inguinal hernia	F.L.—Wound separation
A.K.—Spigelian hernia	J.B.—Wound infection
G.P.—Wound infection	C.G.—Upper intestinal obstruction
R.W.—Pulmonary embolus and stress ulcer	
D.C.—Adhesions causing small bowel gangrene and death (3½ yrs. P.O.)	

surgeon. One day at school he developed abdominal pain while eating a frankfurter. Because of this unfortunate setting surrounding the advent of his abdominal discomfort, he was treated for food poisoning for four days. He subsequently died at home and was found at autopsy to have had a loop of gangrenous bowel secondary to a postoperative adhesion.

Discussion

Transposing the omentum for chronic lymphedema of an extremity was based on the concept that omental lymphatics would re-establish lymphatic flow across the area of lymphatic interruption. Clinical success with this operation by the author and others,[2,6] including published lymphangiograms demonstrating lymphatic reestablishment,[2,6] has confirmed the reasoning behind the procedure. The question now is whether clinical results of omental transposition justify its continued performance.

Since I do not believe omental transposition is a difficult operation to perform and because many, if not most, of the potential surgical problems inherent in the procedure have been worked out, I plan to continue to perform the operation when indicated, especially in patients with chronic lymphangitis since the operation has been most impressive in correcting this problem. However, I have been impressed with favorable reports of simpler operations for chronic lymphedema such as the Thompson operation of a buried dermal flap,[7] and the subcutaneous excision of lymphedematous tissue.[5] If I were asked to recommend an operation for chronic lymphedema by a surgeon with no experience in transposing the omentum, I would be inclined to suggest that one of the above two procedures be performed, since neither operation violates the peritoneal cavity as does omental transposition. If the initial operation for chronic lymphedema proved ineffective, omental transposition could be performed at a later date with the knowledge that a reasonable number of patients might be expected to have a satisfactory response.

The large number of operations devised for improving lymphatic drainage from a chronically lymphedematous limb indicates the lack of a surgical procedure which is consistently effective. Because of the relative rarity of chronic lymphedema, only a few surgeons have been able to develop a sizeable clinical experience with the problem. This has meant that the majority of surgeons who see only an occasional patient with chronic lymphedema, usually must rely upon the reports of others in deciding the best operation to offer their patient. Unfortunately, even surgeons with a relatively large experience with chronic lymphedema don't have enough patients or the inclination to carry out a controlled clinical experiment. This results in the surgeon championing the operation found most effective in his hands without his ever developing sufficient experience with other procedures to test their clinical effectiveness or to learn the operative techniques necessary to minimize their post-operative complications. The author has performed only omental transposition for chronic lymphedema and therefore must accept this criticism. A carefully controlled clinical study which allows objective evaluation by unbiased observers of long-term results of various surgical procedures for chronic lymphedema is truly needed.

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Prolonged Partial Venoarterial Bypass:

Physiologic, Biochemical, and Hematologic Responses

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Prolonged veno arterial extracorporeal bypass (50–80% of cardiac output) was evaluated in normal, unanesthetized sheep. The evaluation protocol included serial measurements of hemodynamics, pulmonary and renal function, serum enzymes to detect organ damage, and detailed studies of coagulation and platelets. Blood exposure surfaces were primarily polyvinyl chloride and silicone rubber. Gas interfaces were carefully excluded with the exception of four experiments utilizing bubble oxygenators. Heparin dose was titrated to maintain activated clotting to two to three times baseline. Characteristics of 48 hour uncomplicated extracorporeal circulation in 8 sheep included normal hemodynamics, mild respiratory alkolosis negligable hemolysis, slight gradual increase in heart, liver, and muscle enzymes. The most significant changes occurred in coagulation and platelets characterized by an initial reduction in coagulation factors with a continued reduction in platelet count and return to normal clotting factors during extracorporeal circulation. This is followed by a two times normal increase in platelets and fibrinogen following extracorporeal circulation.

Prolonged extracorporeal circulation with gas exchange through a membrane oxygenator is a radical but sometimes necessary approach to management of the patient with severe pulmonary insufficiency. Partial veno-arterial cardiopulmonary bypass provides passive support of gas exchange during the period of pulmonary failure and affords active treatment of the lung by reducing pulmonary hydrostatic pressure. Extensive and orderly laboratory investigation in the physiology of prolonged bypass,[3,5,6,10,14,15] membrane oxygenator design,[2,14,15,17] anticoagulation control,[3,10,12,] responses in normal animals,[2,3,6,8,10,14,17] and in patients during open-heart procedures,[7,21] led to the first successful clinical application on this technique reported by Hill, O'Brien and others in 1971.[11] Since that report the technique has been used successfully in at least ten other clinical patients.[12] With widespread clinical application appearing feasible, it is increasingly important to establish the normal responses to prolonged venoarterial bypass in an animal model which resembles the human. This study was undertaken to evaluate and define the responses to prolonged extracorporeal circulation in normal sheep, and to identify the complications, potential risks, and best techniques for clinical application.

Materials and Methods

Partial veno-arterial bypass with a membrane oxygenator was carried out in eight awake normal 50–80 lb farm lambs. Bypass was carried out for 24–48 hours, terminated electively, and the animals followed for two weeks. Measurements were made at regular intervals and full autopsies performed. Data from these studies represent the response of the normal sheep to prolonged bypass.

Eight other sheep died of technical complications after 6–40 hours of bypass. Data from these studies are presented to illustrate the sensitivity of the testing protocol and the potential risks of the procedure. In four sheep prolonged bypass was attempted with a gas-interface (bubble) oxygenator. Data from these studies are presented to compare the variables of gas-interface exposure to the non-gas interface system.

Sheep were anesthetized with Ketamine, 10 mg/kg intravenously, with doses repeated as necessary during the cannulation procedure. Sheep do very well under Ketamine and awake promptly following anesthesia. Further sedation or analgesics were not necessary. After anesthesia ap-

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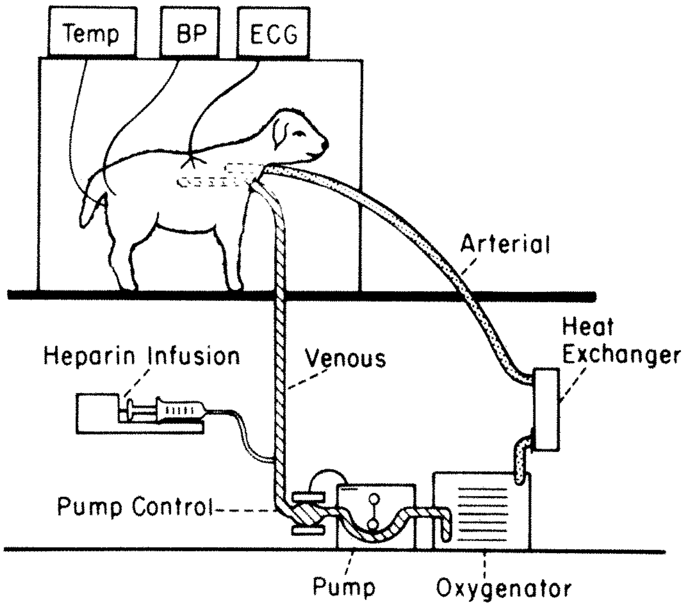

FIG. 1. Diagram of the extracorporeal circulation circuit.

propriate catheters and electrodes were placed for femoral artery pressure, EKG, and temperature monitoring. The right atrium was catheterized using the largest polyvinyl catheter that would pass through the right internal jugular vein. Blood was returned to the carotid artery or the femoral artery which was ligated distally (Fig. 1). During bypass the sheep were allowed to sit and stand in a small restraining cage and ate and drank freely. A brief Ketamine anesthetic was given for decannulation at the termination of bypass. At the conclusion of bypass the cannulated vessels were ligated and incisions closed. Keflin® was administered intermittently during the procedure. No significant infections occurred in the catheterization sites. The bypass circuit was composed primarily of polyvinyl chloride ⅜″ tubing and polycarbonate connectors. Venous blood drained directly to a servo-regulating ventricle or roller pump on the floor, and was pumped through the oxygenator (with the exception of the bubble oxygenator which was incorporated on the venous side of the circuit). The .4m^2 toroidal membrane oxygenator[2] (four animals), two 3m^2 Landé-Edwards membrane oxygenators[5] in parallel (four animals), the Bentley Pediatric Temptrol ® oxygenator and the Travenol® bubble oxygenator were used in this system. The oxygenators were ventilated with 95% O_2, and 5% CO_2. The entire extracorporeal circuit was primed and rinsed twice with Ringer's lactate solution, then filled with freshly drawn nonhemolyzed heparinized sheep blood, warmed to 37C, and buffered to pH 7.4. The priming volume was approximately 2 L. Some crystalloid solution remained in the bypass circuit and the hematocrit of the primed extracorporeal circuit was 18–25%. Prior to placement of cannulas heparin, 2 mg/kg, was given as a single dose intravenously and bypass was instituted. Flow rates were gradually increased until the desired flow rate was obtained, usually 80 cc/kg/min. All tubes were secured in place and the animal was returned to its cage and was allowed to awaken and move about during the remainder of the experiment. Heparin solution was infused continuously into the bypass circuit to maintain the activated clotting time between two and three times baseline. Whole blood activated clotting time (ACT)[1] was measured hourly and heparin dose adjusted appropriately. No drugs were given to reverse the heparin effect at the end of bypass.

Blood pressure, pulse, respiration, temperature, arterial, venous and oxygenator PO_2, PCO_2, and pH were measured and recorded at frequent intervals. Coagulation screening tests, specific factor assays, platelet counts, total plasminogen-activity, and fibrin (ogen) degradation products were measured prior to anesthesia, at regular intervals during bypass, and at up to two weeks following bypass. Total plasminogen was assayed by the caseinolytic method[4] and the euglobulin lysis time.[13] Fibrin (ogen) degradation products were determined by immunoprecipitin methods, utilizing anti-human fibrinogen.[20] Platelet adhesiveness, aggregation, and Factor III were measured in one experi-

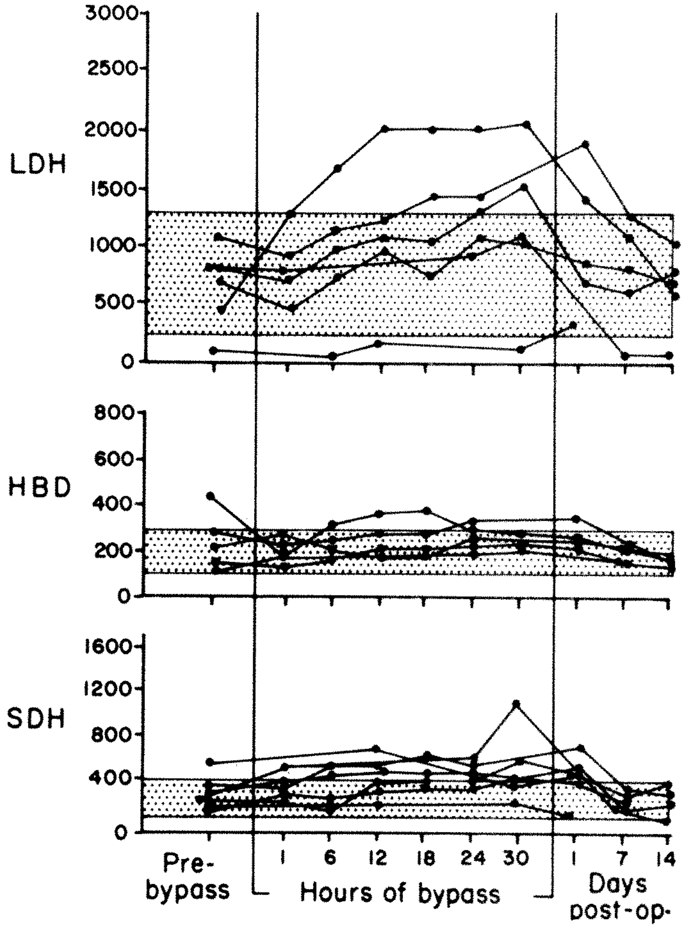

FIG. 2. Serum enzyme changes during uncomplicated extracorporeal circulation in eight sheep.

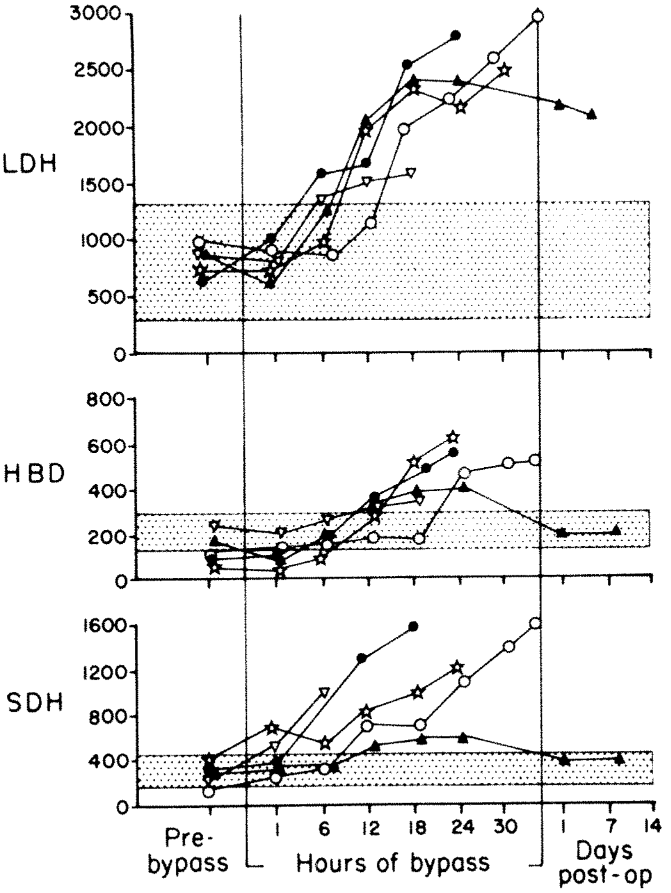

FIG. 3. Serum enzyme changes during extracorporeal circulation with complications associated with tissue damage (five representative sheep).

○ = volvulus, intestinal necrosis
△ = bubble oxygenator, survivor
▽ = low heparin, diffuse emboli
● = Cardiac damage from catheter
☆ = cardiac damage from catheter

ment. Specific organ perfusion and damage were assessed by a regular measurement of serum enzymes: sorbitol dehydrogenase (liver) a-hydroxy-butyrate dehydrogenase, (heart), and lactic dehydrogenase (most tissues). Blood urea nitrogen, glucose, electrolytes, and plasma hemaglobin were measured at regular intervals as were white blood cell count and differential, hemoglobin and hematocrit.

Results

During uncomplicated bypass in normal sheep hemodynamics and perfusion remained normal during extracorporeal circulation at 50–100 cc/kg/min. Normal sheep cardiac output is approximately 120 cc/kg/min. Mean arterial pressure stayed above 100 mm Hg and pulse ranged 90–116 beats per minute. The bypass flow was adjusted so that the left ventricle ejected and established a pulsatile flow contour with every beat. Other studies in our laboratory have shown that higher flows on bypass will result in incomplete emptying of the left ventricle with ejection occurring only occasionally. This may not be necessarily detrimental. The bypass flows in this study were elected to maintain normal pulsatile peripheral perfusion and were calculated to approximate the level of bypass flow which would be necessary to supply total extracorporeal gas exchange in the face of pulmonary insufficiency. Hyperventilation with mild respiratory alkalosis occurred throughout the bypass in all animals. Hypotension with metabolic acidosis did occur in some lambs with complications associated with poor venous return and decreasing bypass flow. All the bubble oxygenator lambs developed progressive hypotension, three died during 12 hours, one survived 24 hours of bypass without residual damage.

There was no significant change during ECC in serum sodium, potassium, chloride, carbon dioxide content, bilirubin, or total protein. Blood urea nitrogen increased from 39 to 59 mg% (average). Plasma hemoglobin at the end of bypass was 8 mg%, average (6 to 33 mg% range). The surviving animal with the bubble oxygenator developed azotemia (BUN 61 mg%) and hemolysis (plasma hemoglobin 104 mg%). Two lambs in the complication group had transfusion reactions as a result of using a donor that had been previously sensitized. Both showed hemolysis promptly following transfusion of donor blood (plasma hemaglobin 84 and 183 mg%).

Serial measurements of LDH, HBD, and SDH showed progressive rise during extracorporeal circulation to approximately twice baseline levels but generally remained below the upper limits of normal for sheep in our laboratory

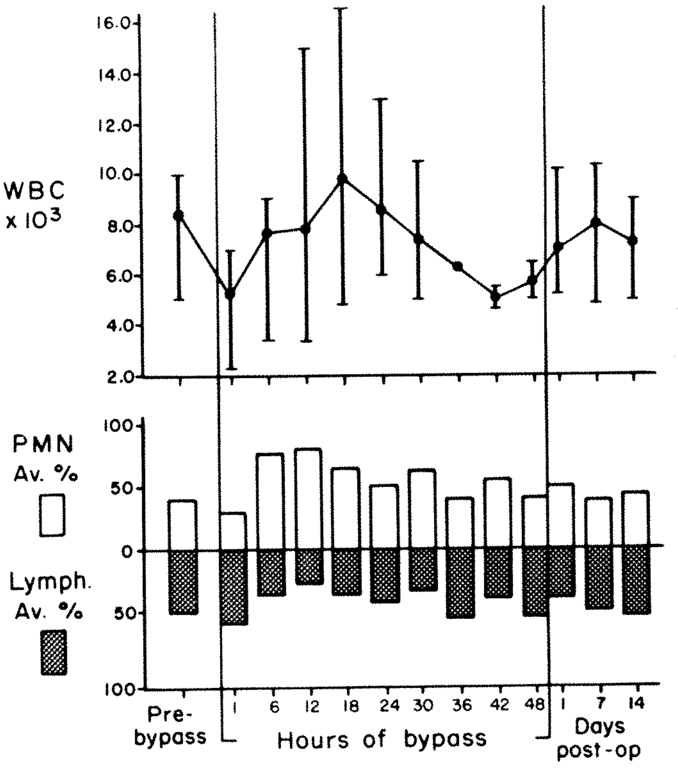

FIG. 4. Leukocyte changes during uncomplicated extracorporeal circulation (eight sheep).

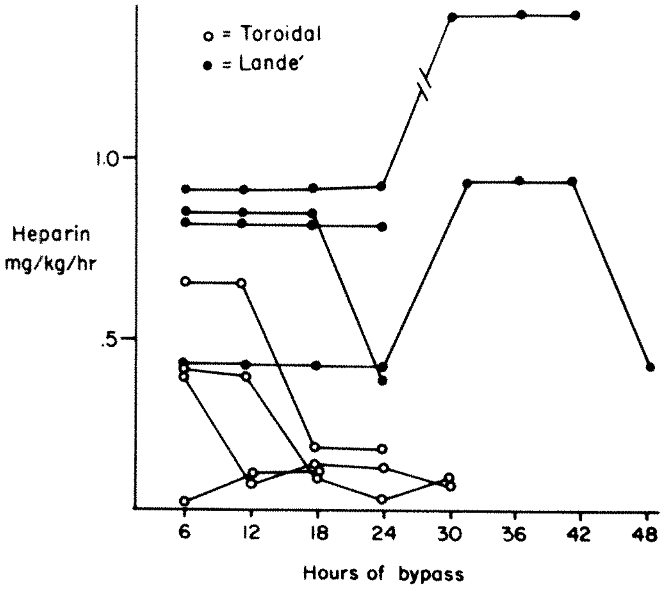

FIG. 5. Heparin dose during uncomplicated extracorporeal circulation in eight sheep.

(LDH 1350, SDH 450, HBD 292) (Fig. 2). No organ damage was detected at autopsy in these animals.

In the complication group, when liver damage from embolization occurred in one lamb, SDH levels rose from 300 to 1600 in 12 hours. When cardiac damage from a catheter inadvertantly placed in the coronary sinus occurred HBD levels rose from 75 to 600 units in 24 hours. Levels of LDH, HBD and SDH had increased five fold during a 40 hour bypass which appeared to be uncomplicated. Autopsy disclosed a volvulus with extensive bowel infarction. The bubble oxygenator experiments showed a two fold and three fold rise in all enzyme levels. These changes in tissue specific enzymes are outlined in Fig. 3. These findings demonstrate that tissue specific enzymes are a helpful retrospective analysis of the bypass course and identify the time sequence of early organ damage which can be correlated with other events.

Hematological studies showed a moderate leukocytosis during the first 24 hours of bypass which was characterized primarily by increase in the granulocytic series as shown in Fig. 4. There was a gradual drop in hematocrit and hemoglobin contration which was related to sampling. Freshly drawn sheep blood was used for transfusion on several occasions when hypovolemia occurred due to sampling. Bleeding from the animal did not occur except in the bubble oxygenator experiments.

The heparin in dose required to maintain the ACT two times baseline varied between 0.2 and 1.0 mg/kg/hr. (Fig. 5). Dosage was somewhat less for the toroidal oxygenator during the second 24 hours of bypass. When the ACT was inadvertantly allowed to fall to normal levels in two animals, clotting, diffuse embolization and death occurred.

The most striking changes during long term bypass occurred in the coagulation system. The changes in coagulation are outlined in Figs. 6–8. In order to study conventional screening tests and specific factor assays it was necessary to inactivate the heparin in the blood samples with (Polybrene®) (hexamethadrine). This was done by adding 50 μgm of Polybrene® for each 1 cc of blood sample. We have previously demonstrated that this amount of Polybrene® neutralized the amount of heparin expected relative to the infusion rates. An excess of Polybrene® in this dosage does not affect coagulation assays by itself. In our studies it was found that all the coagulation factors decreased by 30–40% promptly after institution of bypass. Much of this is due to dilution effect. Coagulation factors in the prime were approximately 30% of control sheep levels. After this initial decrease the clotting factors gradually returned toward normal, reaching normal values by 24 hours and remaining at that level throughout bypass. These moderate changes in clotting factors were not detected by conventional screening tests (Fig. 6). The platelet count also dropped by 30% at the institution of bypass and continued to drop slowly at the rate of approximately 10% of the remaining platelets per hour as long as bypass was continued. Platelet function was studied in one animal. Platelet Factor III activity[9] and platelet adhesiveness to glass beads[19] were both lost during bypass. This appears to be an effect of heparinization and these assays can be returned to normal by addition of Polybrene® to the blood sample. Heparin appears to be an inhibitor of platelet adhesiveness and Factor III release, or at least an inhibitor of the conventional assays of platelet function. These interrelationships are undergoing further investigation in our laboratory. Assays of total plasminogen activity showed no significant levels of fibronolytic activity in normal sheep blood or no significant increase during prolonged bypass. The sheep is known to have a very inac-

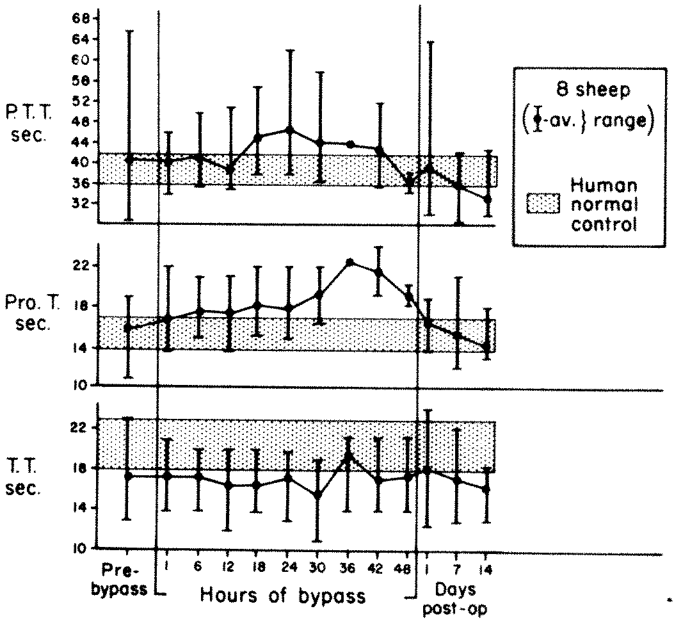

FIG. 6. Coagulation screening tests during uncomplicated extracorporeal circulation (eight sheep)

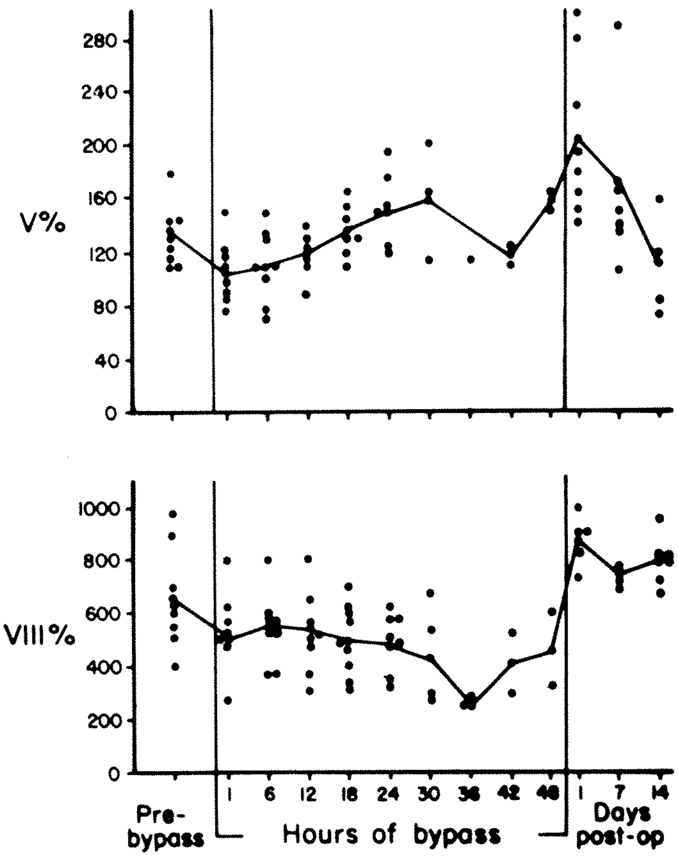

FIG. 7. Factor V and VIII during uncomplicated extracorporeal circulation (eight sheep)

was found. In other animals in which the venous catheter was inadvertantly placed in the coronary sinus, myocardial hemorrhage associated with low cardiac output was found.

Discussion

Although we[3] and others[6,17] have previously used the dog as an experimental model for prolonged extracorporeal circulation, the active nature of that animal and the very active fibrinolytic system prompted the search for a more sensitive and a more human-like experimental preparation. The sheep has served this function extremely well. In addition to being anatomically and physiologically similar to the human, the coagulation mechanism of the sheep is quite valid for studies of extracorporeal circulation. One could imagine that the relatively high numbers of platelets and low fibrinolytic activity have been selectively bred into sheep during annual shearing over the last several centuries. At any rate, the sheep provides a severe test of thrombogenicity in an extracorporeal circuit. In addition sheep are docile and extremely easy to work with in a prolonged unanesthetized state.

Most of the findings in this study are similar to those previously found in patients,[11,12,15,18] and other sheep experiments.[8,14] In essence there are no major changes in hemodynamics, organ function, hemolysis, fluid and electrolyte balance, and no evidence of tissue damage measured by enzyme assay or at autopsy. Major changes with prolonged partial bypass occurred almost exclusively in the tive fibrinolytic system[16] and our data corroborate those observations. Fibrin(ogen) degradation products were not detected to a significant degree. Animals perfused with a bubble oxygenator showed similar, but more exaggerated changes in coagulation (Fig. 9). Platelets were nearly absent from the circulating blood within 12 hours of the institution of bypass with a bubble oxygenator and remained at very low levels during the next 12 hours in the one animal that survived.

Following bypass a significant hypercoagulable state occurred, with platelet count and fibrinogen level rebounding to two to three times baseline levels at one week after bypass.

The bypass system used in these experiments was safe and reliable. No significant mechanical malfunctions occurred in any of the experiments. Oxygenator performance with either the Landé-Edwards or the Toroidal membrane oxygenator did not change during these bypass experiments. Blood leaving the oxygenator was always fully saturated and CO_2 removal was excessive unless 5% CO_2 was used as the ventilating gas.

On autopsy the lungs, heart, brain, kidney and liver of surviving uncomplicated animals were normal. In two animals whose heparin doseage was inadvertantly omitted and clotting time returned to normal, systemic embolization

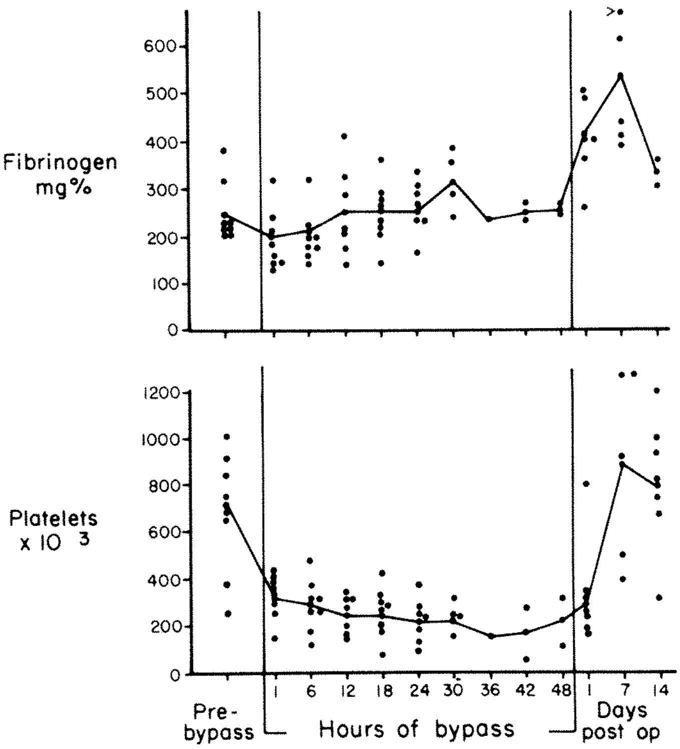

FIG. 8. Fibrinogen and platelet count during uncomplicated extracorporeal circulation (eight sheep)

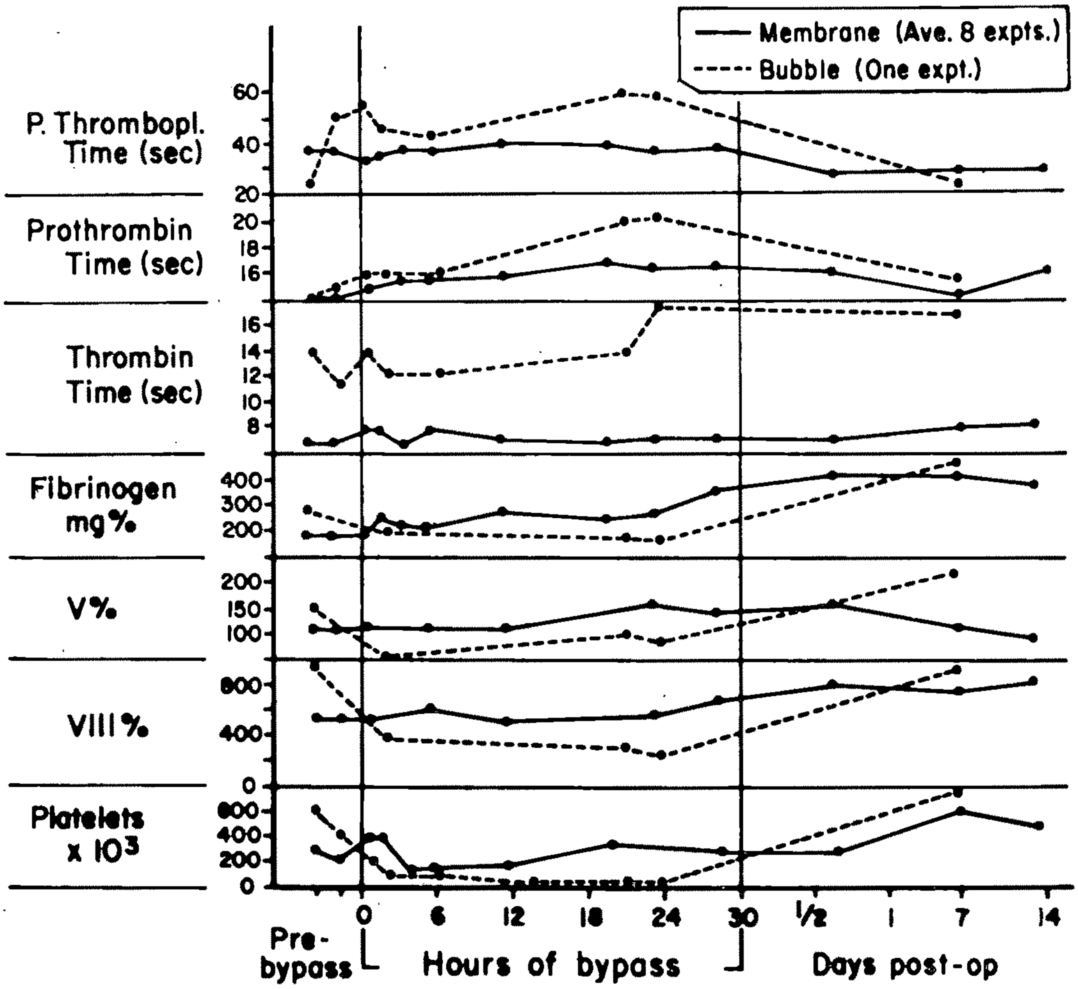

FIG. 9. Coagulation changes during extracorporeal circulation with a gas interface (bubble) oxygenator. Values for one 24-hour bypass sheep are compared to average values for eight sheep perfused with membrane oxygenators.

coagulation system and specifically in platelet numbers and function. Control of coagulation in the extracorporeal circuit has been very satisfactory with the heparin titration method proposed by Bartlett and Drinker in 1969.[3] The heparin dose required to maintain the activated clotting time between two and three times normal was approximately 0.5 mg/kg/hr. This was the same for all types of oxygenators tested although the heparin requirement for the toroidal oxygenators appeared to be somewhat less than the Landé-Edwards (Fig. 5). The continuous gradual dimmunition in platelet count has been reported by other investigators.[5,6,10,14,17] The fate of the disappeared platelets is open to question. There were no grossly obvious fibrin or platelet accumulations in the extracorporeal circuit at the end of bypass. We have no evidence to support or deny the observation of de Leval and others that platelets may be trapped in the liver.[5] Hicks[10] suggested that platelets aggregate in response to any foreign surface, are bound in the reticuloendothelial system, disaggregate and recirculate. The rebound effect in platelet count and fibrinogen level is quite marked and suggests a propensity to thromboembolism after a period of prolonged bypass which might be important clinically.

Use of venoarterial bypass is definitely preferable to veno-venous bypass for pulmonary or cardiac support. Pulmonary artery pressure significantly decreases during veno-arterial bypass facilitating removal of fluid from the lung interstitium. The high flow rate required for extracorporeal gas exchange support can be achieved without the possibility of re-circulation which invariably occurs at high flow rates with a veno-venous bypass.[8] The use of venoarterial bypass also permits a variety of techniques for active treatment of the lung during bypass such as inflation and lavage with antibiotics or mucolytic containing fluids and continuous positive pressure inflation without ventilation.

Conclusions

Partial veno-arterial bypass using these techniques can be done safely and routinely for 48 hours in normal sheep without significant blood or organ damage. The awake sheep model and evaluation protocol described here provides an effective model for the study of prolonged extracorporeal circulation. Characteristics of 48 hour uncomplicated extracorporeal circulation in normal sheep include normal hemodynamics, mild respiratory alkalosis, negligible hemolysis, slight gradual increase in heart, liver, and muscle enzymes. There is an initial reduction in coagulation factors with a continued reduction in platelet count and a return to normal clotting factors during extracorporeal circulation, followed by two times normal increase in platelets and fibrinogen after extracorporeal circulation. Initial studies indicate that platelet aggregation is unchanged during bypass; platelet adhesiveness and platelet Factor III release are both inhibited by low doses of heparin.

Acknowledgments

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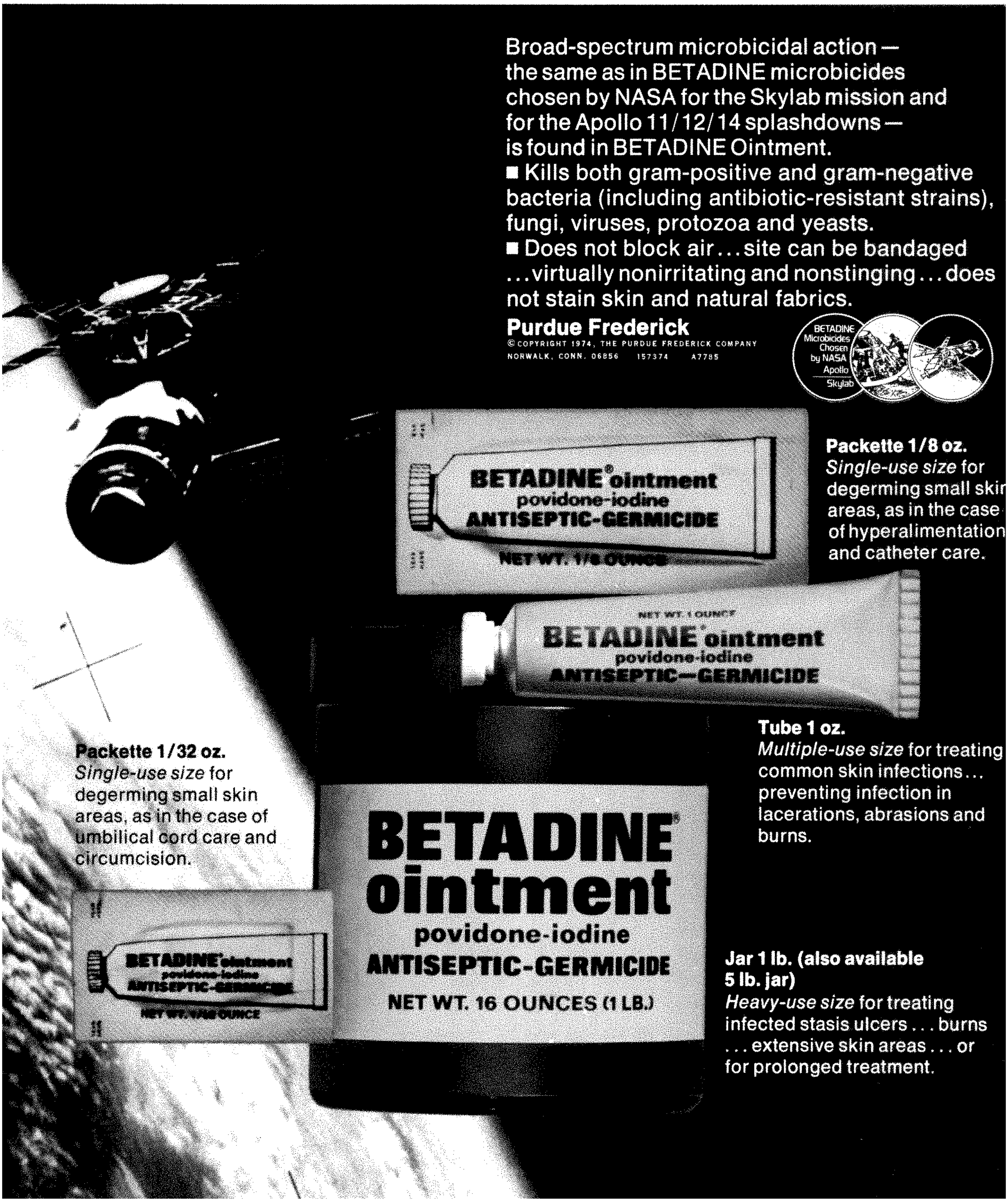

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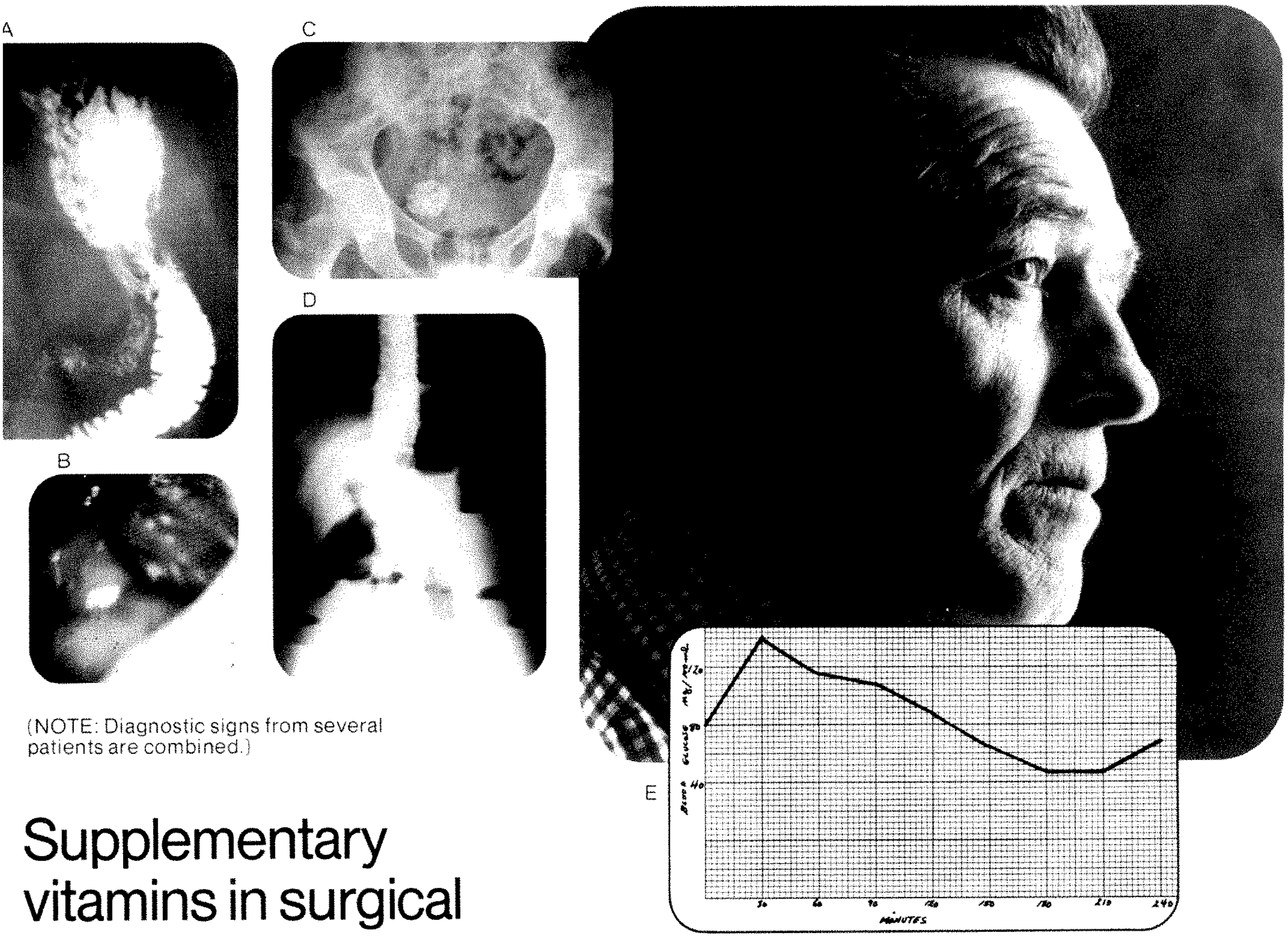

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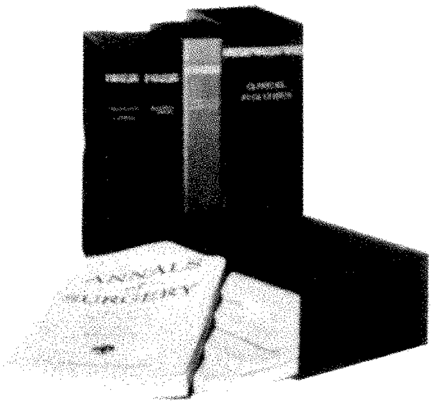

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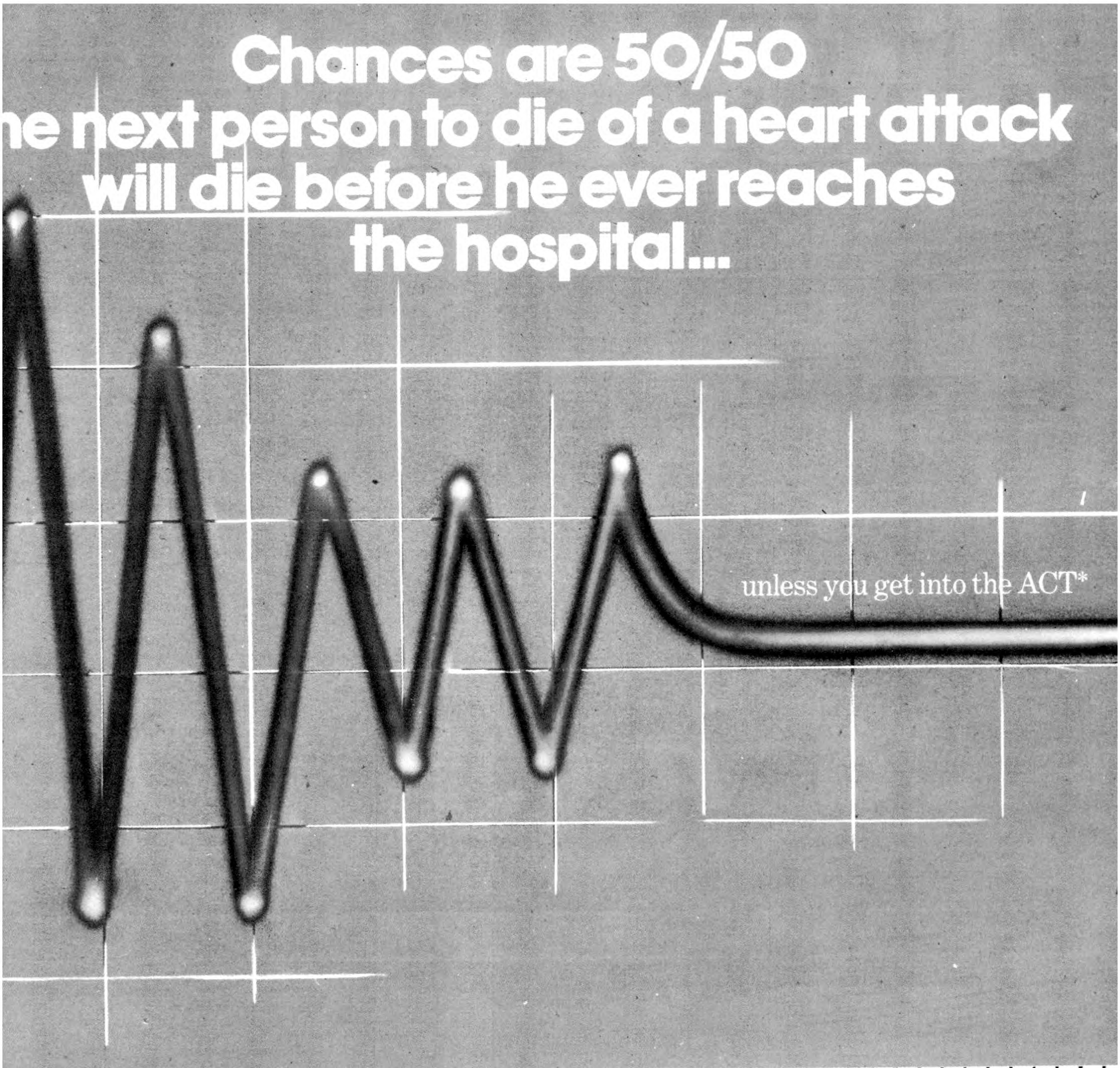
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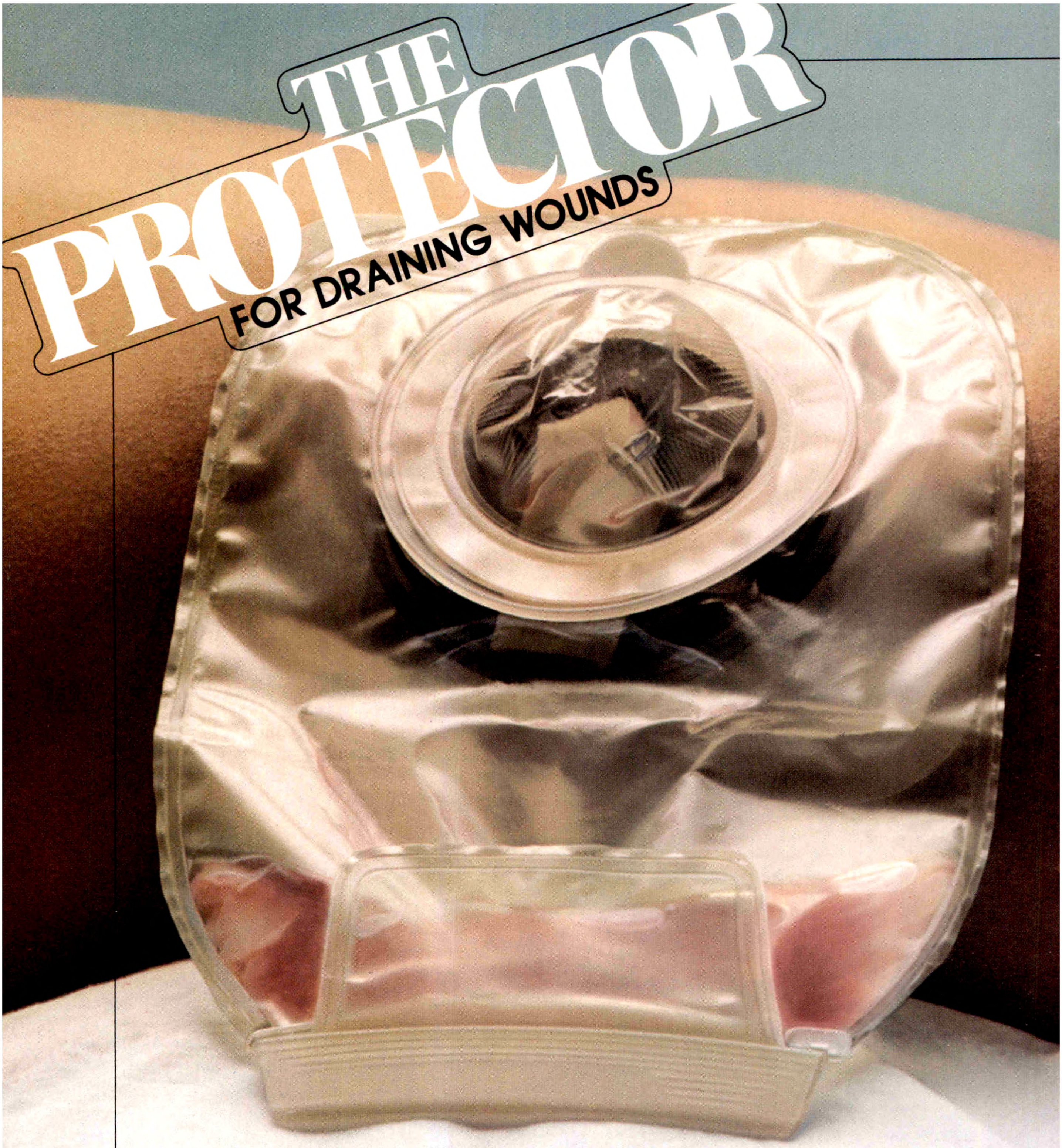

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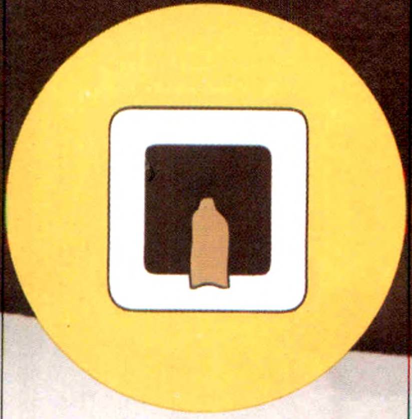

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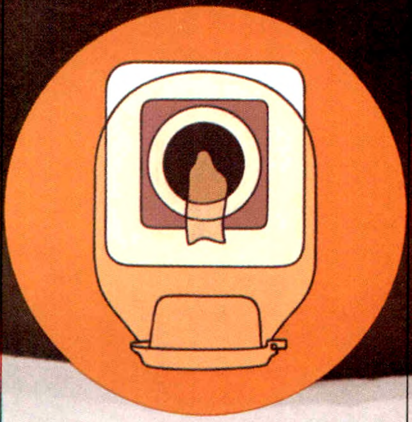

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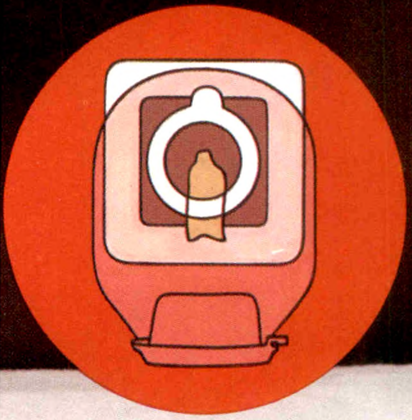

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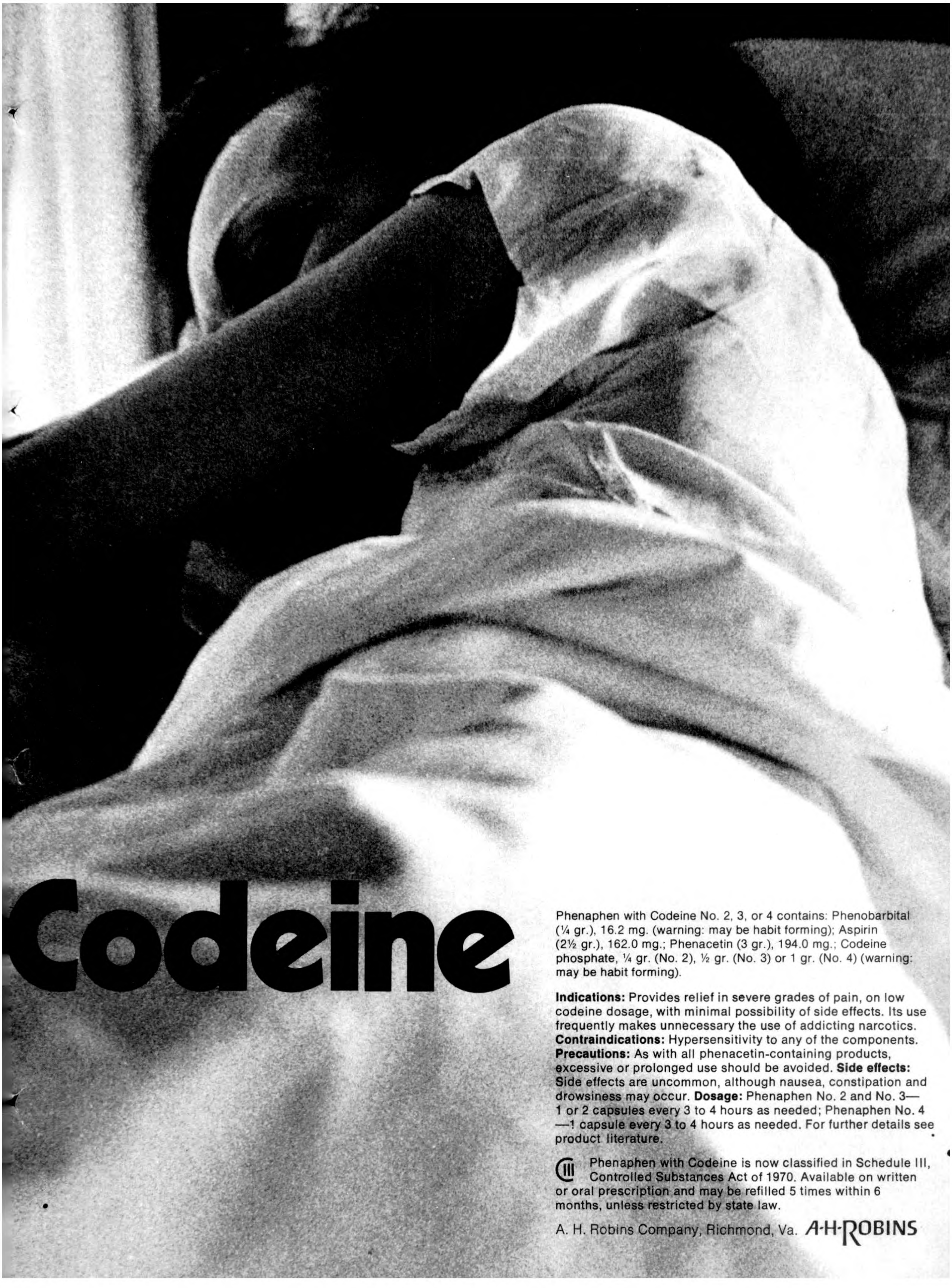

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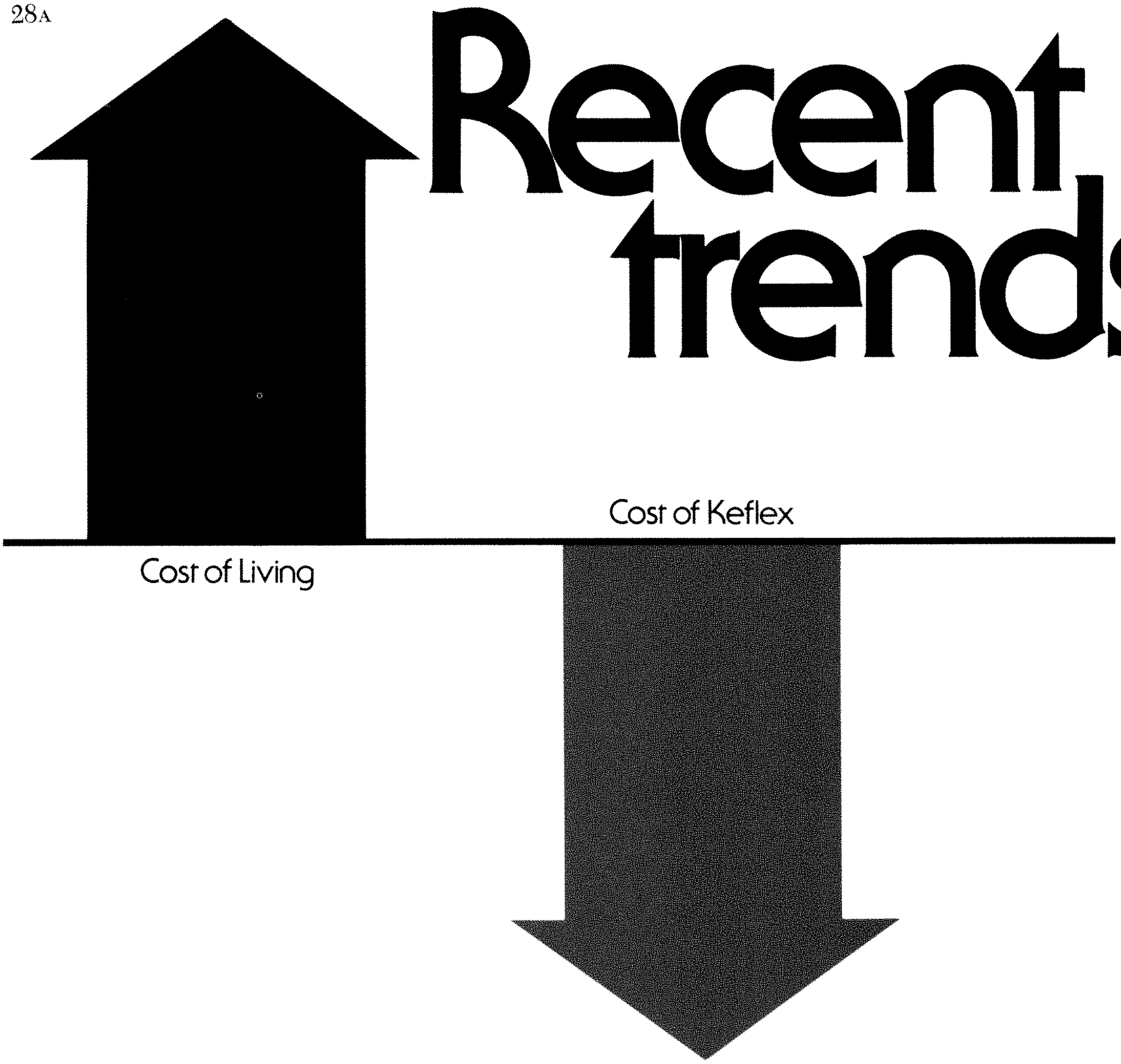

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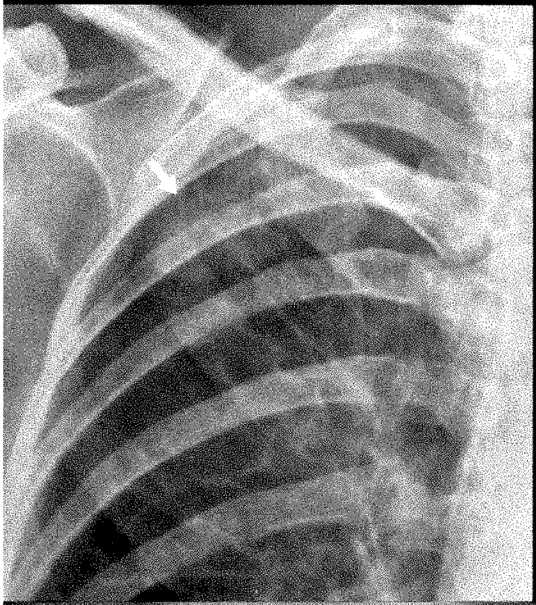

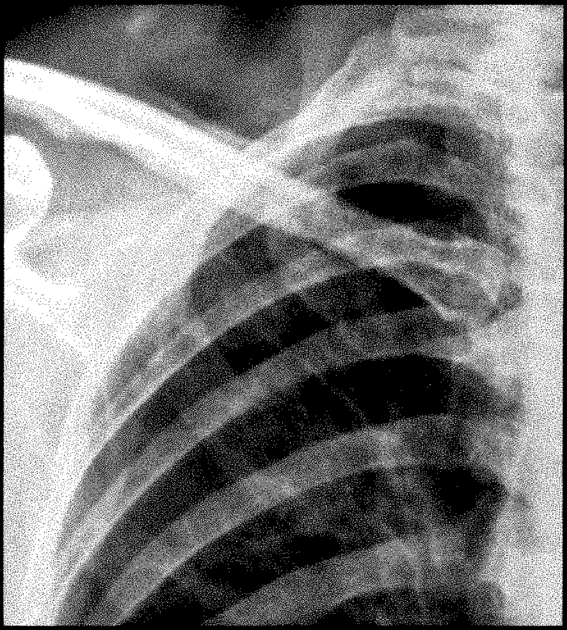

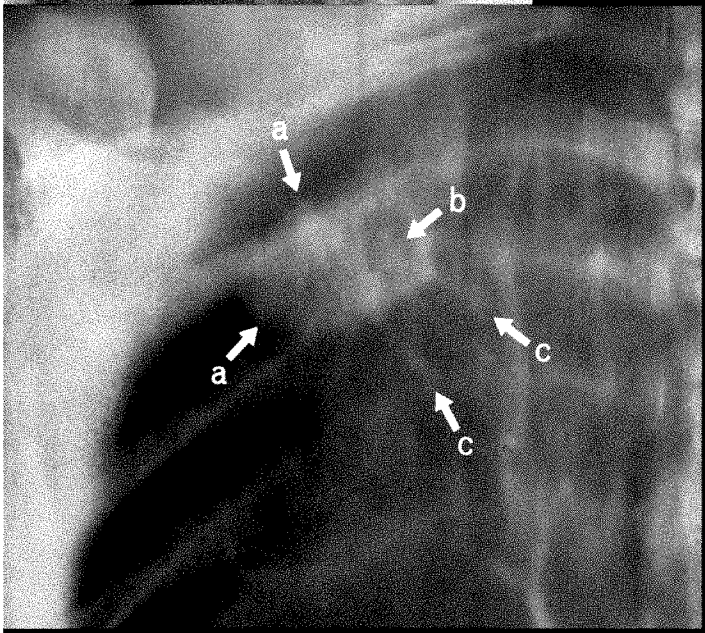

Case I—This 45-year-old lady had a mild cough for several weeks; there were no other subjective or objective clinical findings.

The first roentgen examination of her chest, Fig. A, revealed an ill-defined mass in the right upper lobe (arrow), which the radiologist thought compatible with early bronchogenic carcinoma. The patient's physician was not convinced.

Three months later, Fig. B, the lesion seemed less well defined.

At the insistence of the radiologist, tomographic studies were made, Fig. C, which revealed an irregular mass (a), an eccentric cavity with a relatively thick wall (b), and fine pseudopods (c), all hallmarks of primary lung malignancy.

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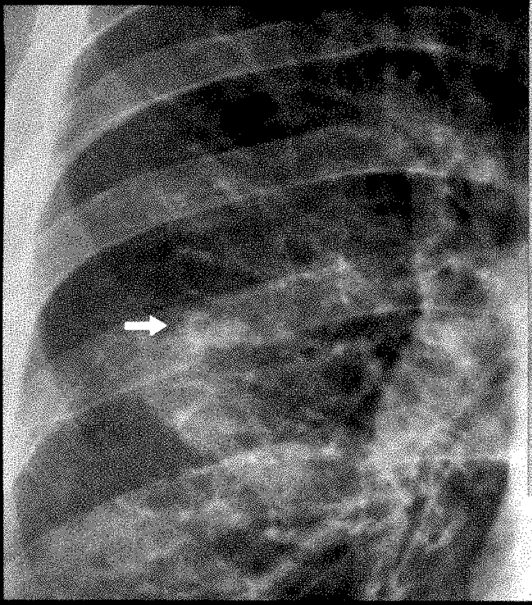

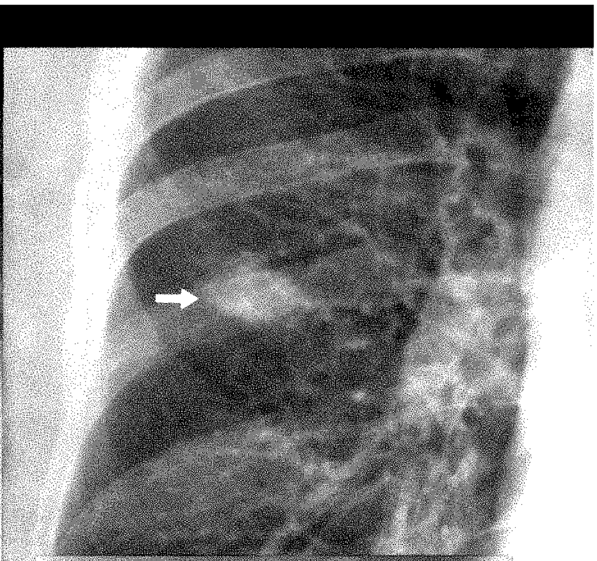

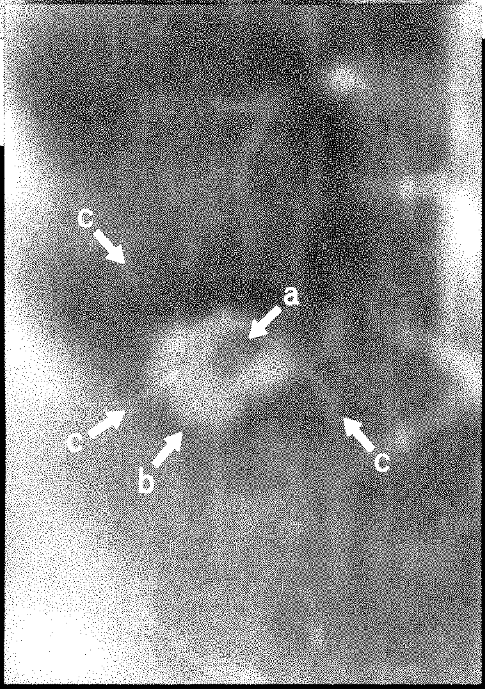

Case II—This 54-year-old man had no clinical complaints; his roentgen study was part of a routine clinical examination.

The patient's first roentgenogram, Fig. A, was considered to be within normal limits except for a healed scar (arrow) in the right lung.

Three years later the patient had another routine clinical examination. He was still symptom free. At this time, Fig. B, the "scar" in his right lung looked more like an irregular mass (arrow). Any doubt concerning its malignant nature was dispelled by the tomographic study, Fig. C, which revealed a thick walled cavity (a) that was situated eccentrically in an irregularly lobulated mass (b) and from which radiated pseudopods (c).

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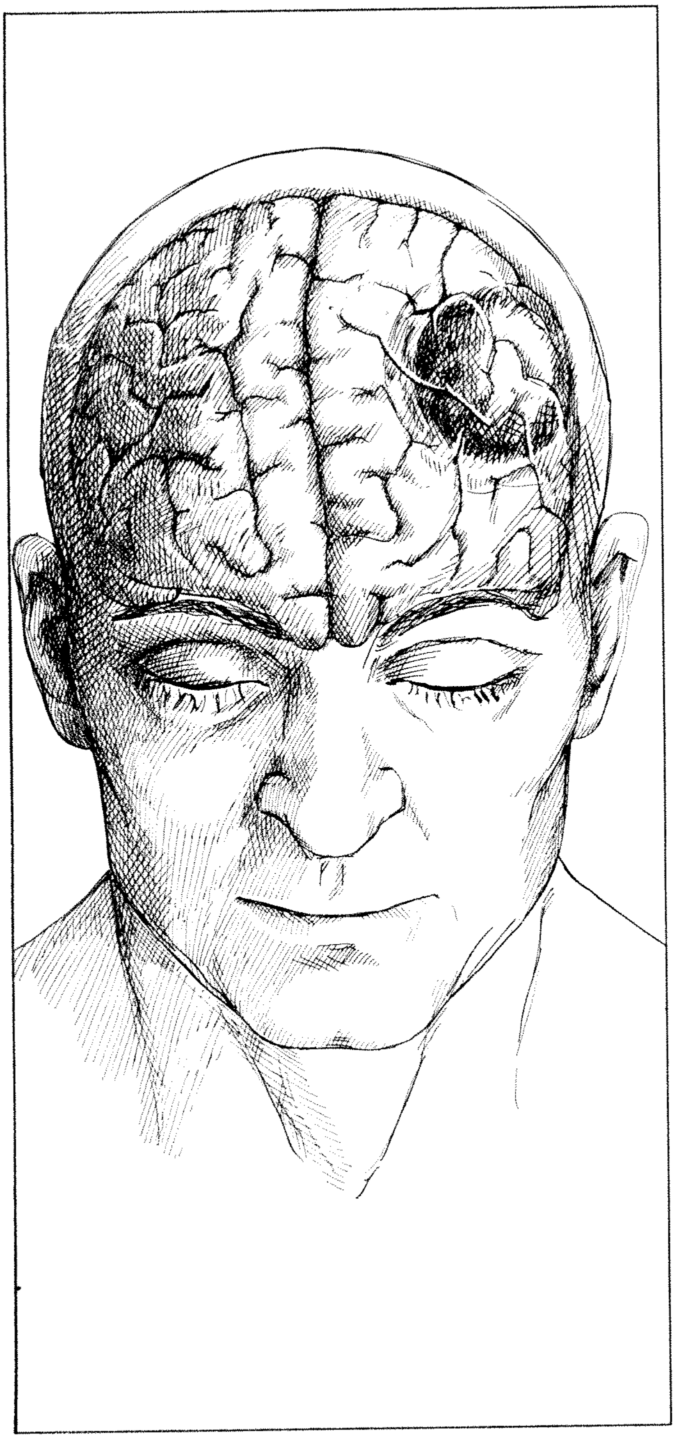
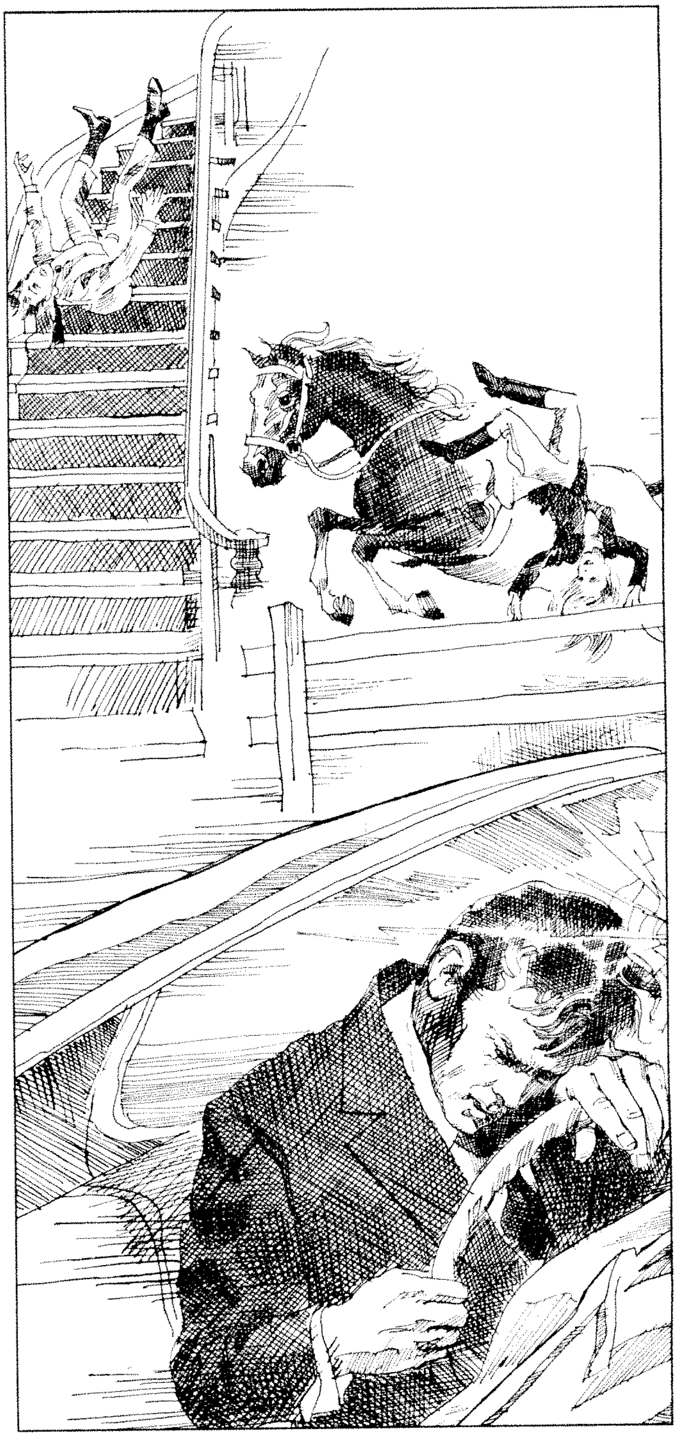
cerebral

expect it as a possible complication of primary or metastatic brain tumor.

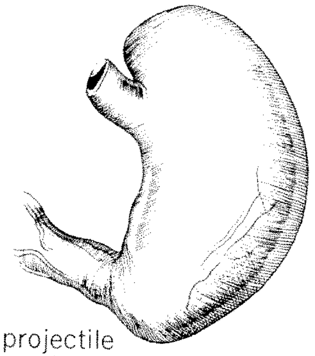


expect it in the presence of severe head injury.

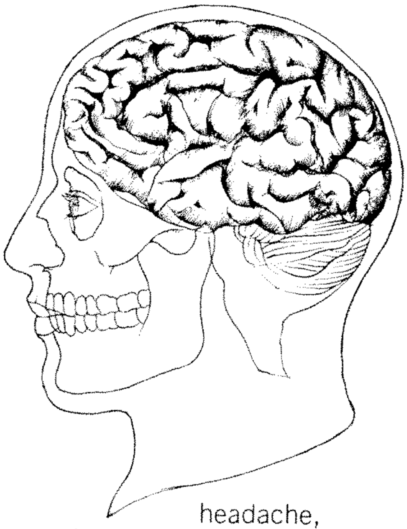


edema*

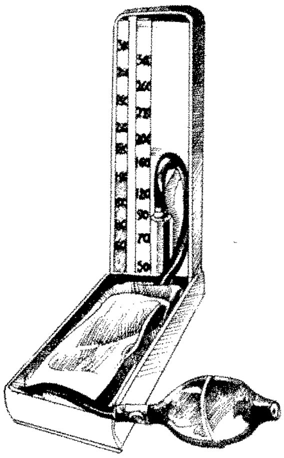
suspect it in the presence of signs and symptoms such as these:



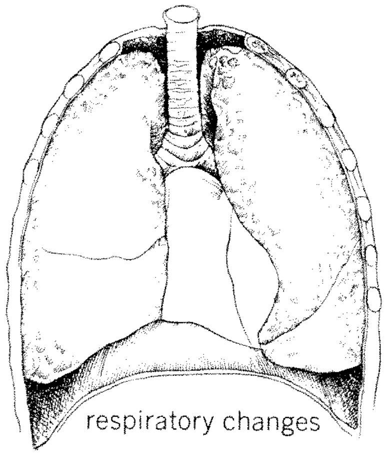
projectile vomiting



headache, altered consciousness

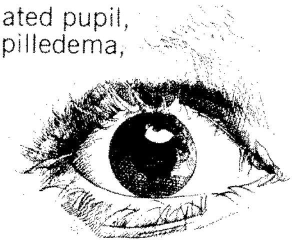


increased blood pressure

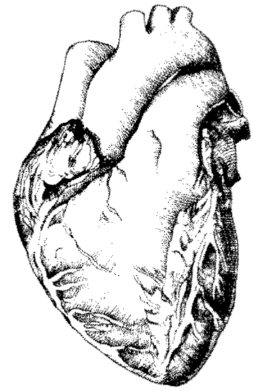


respiratory changes

dilated pupil, papilledema,



unilateral or bilateral abducens palsy



bradycardia

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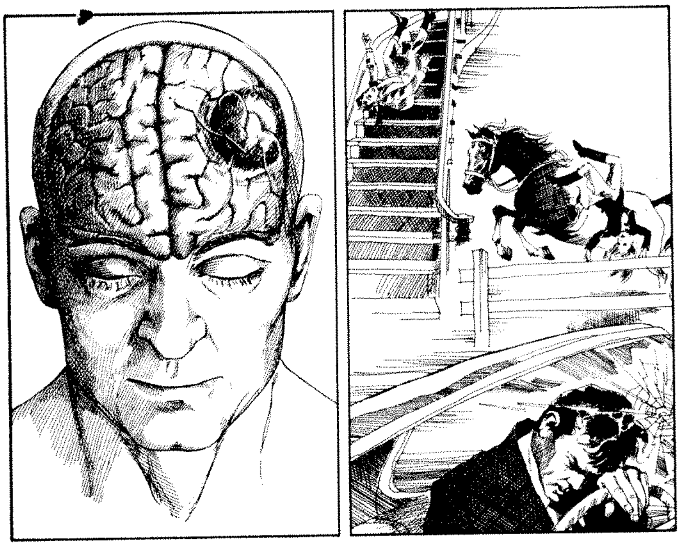

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Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

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Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: Oral and Parenteral Therapy—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

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Prolonged Survival of Renal Allografts in Outbred Rabbits Treated with Donor Specific F(ab')$_2$ Alloantibody

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Renal allograft survival was prolonged in rabbits, a species in which antibody mediated hyperacute rejection can occur, by administering large quantities of donor specific F(ab')$_2$ alloantibody. In 13 control animals, onset of uremia with histological evidence of rejection occurred at a mean of 6.0 days. Eight of eight rabbits actively immunized and seven of nine rabbits passively immunized with unmodified donor specific IgG alloantibody hyperacutely rejected an allografted kidney. Four rabbits treated with non-specific F(ab')$_2$ for one week acutely rejected an allografted kidney at a mean of 6.2 days. In 12 recipient rabbits receiving 100-500 mg of donor specific F(ab')$_2$ alloantibody for a mean of 8.5 days, onset of uremia was delayed to a mean of 14.5 days following transplantation. Recipients were selected so that the donor specific F(ab')$_2$ alloantibody employed had no activity against recipient antigens. This selection maximized the antigenic difference between the donor and recipient, and also assured us that the donor specific F(ab')$_2$ was directed against antigens present in the donor but absent in the recipient. Passive administration of donor specific F(ab')$_2$ allowed antibody mediated suppression of a specific immune response to occur without risk of hyperacute rejection. However, the onset of rejection could not be delayed indefinitely by this treatment. The experimental conditions employed and the difficulties encountered closely resemble those which will occur for clinical utilization of passive immunological enhancement.

PROLONGED SURVIVAL (immunological enhancement) of rat renal allografts can be achieved by passive transfer of alloantibody directed against donor antigens.[10,23,33] The rat kidney seems peculiarly unsusceptible to the detrimental effects of antibody. In most species,[8,17] including man,[15,16] an allografted kidney is rejected hyperacutely when exposed to alloantibody directed against donor antigens. In these species hyperacute rejection is mediated through complement fixation by alloantibody. Therefore, investigators have removed, by pepsin digestion, that part of the immunoglobulin molecule responsible for complement fixation (the Fc portion). They have used the resultant F(ab')$_2$ fragment which cannot fix complement in attempts to allow enhancing properties of alloantibody to be expressed in primates,[18,24] dogs,[1,38] and rabbits.[12,13] Although hyperacute rejection of renal allografts has been prevented by administration of F(ab')$_2$ alloantibody in the monkey,[18] dog,[1,38,39] and rabbit,[12,13] graft survival has been prolonged only minimally or not at all, unless immunosuppressive drugs were also administered.[38,39] In these experiments by other investigators the use of outbred species made it difficult to employ alloantibody specific for all the donor-recipient antigenic disparities. Also, inadequate doses of F(ab')$_2$ alloantibody may have been employed. F(ab')$_2$ has a shortened half life as compared to intact IgG,[32] and F(ab')$_2$ has a decreased effectiveness as a suppressor of a specific immune response as compared to intact IgG antibody.[29]

In the experiment reported here, we performed renal allografts in rabbits and administered large quantities of F(ab')$_2$ obtained from hyperimmune sera directed specifically against donor antigens. By assuring that the alloantisera from which the F(ab')$_2$ was derived had no cytotoxic activity against recipient lymphocytes, we increased the likelihood that the F(ab')$_2$ was directed against most of the antigens present in the donor but absent in the recipient. These studies show that donor specific F(ab')$_2$ alloantibody fragments can (when administered frequently and in high doses), delay the onset of rejection in some rabbits, but only for as long as it is administered. Once administration is discontinued the rejection process ensues.

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Materials and Methods

Animals

We used outbred New Zealand White (NZW) strain, and Dutch strain rabbits as recipient and donor rabbits respectively.

Preparations of Donor Specific Alloantibody

Alloantibody to specific Dutch kidney donors was produced in specific third party NZW rabbits. Immunization monthly for three months with full thickness skin grafts implanted subcutaneously was followed by intravenous injections of *1–4* × 10^8 donor spleen cells. Thereafter the rabbits were bled (30–50 ml one to three times weekly for 6–16 months) until we had collected 500–1500 ml of antisera against each donor rabbit. We performed skin grafts monthly throughout the course of bleeding to maintain a high alloantibody titer. We chose alloantisera with lymphocytotoxic titers against specific donor cells ranging from 1 : 16 to 1 : 128, as measured by a modification of the method of Amos *et al.*[2] Donor specific IgG alloantibody was then purified from the selected antisera by ammonium sulfate fractionation and DEAE 52 column chromatography.[36]

F(ab')$_2$ Preparations

The donor specific IgG alloantibody was concentrated to 20 mg/ml, dialysed against 0.1 M acetate buffer, pH 4.2, and then subjected to pepsin digestion according to Holter's modifications[12] of Nisonoff's technique.[25] Digestion for ten hours with a pepsin:globulin ratio of 1 : 50 was followed by a two-hour boost of pepsin at a ratio of 1 : 100 before the reaction was stopped by raising the pH to 8.0.

In pilot experiments with rabbit IgG, we had tried other pepsin digestion protocols. After digestion for 18 hours without a pepsin boost, residual IgG was present and had to be separated from F(ab')$_2$ by Sephadex G-200 column chromatography, with considerable loss of F(ab')$_2$ from the separation procedure. Digestion for 24 hours eliminated all IgG and the need for separation chromatography, but it also resulted in partial destruction and decreased yield of F(ab')$_2$.

Holter's technique[12] resulted in complete digestion of IgG with a maximum yield of F(ab')$_2$. The molecular weight of the end product was 100,000 or less compared to a predigest weight of 160,000, as estimated by gel filtrations on a precalibrated G-200 superine Sephadex column.[3] Goat antiserum prepared against the Fc fragment of rabbit IgG (supplied by Dr. Richard Hong, Department of Pediatrics, University of Wisconsin) and able to detect IgG at concentrations as low as 0.025 mg/ml in standard radial diffusion immunoassay[19] did not react with the largest molecular weight end product of pepsin digestion. Goat anti-rabbit IgG antiserum was reactive with the F(ab')$_2$ product of pepsin digestion.

The pepsin digest was adjusted to isotonicity with saline, sterilized by passage through a millipore filter, and stored at 4C.

Renal Transplantation

Our technique of kidney transplantation[14,20] was modified after that of Holter *et al.*[12] Briefly, the left kidney of the donor rabbit was transplanted orthotopically to a recipient rabbit subjected to immediate bilateral nephrectomy. The renal arteries were anastomosed end-to-end with 8–0 nylon suture, and the donor renal vein with an attached patch of vena cava was anastomosed end-to-side to the recipient vena cava with 6–0 silk. The donor and recipient ureters were approximated over a 1.0 cm polyethylene tube stint.

In successful transplants, the blood urea nitrogen (BUN) concentration of the recipient was no greater than 60 mg per cent by the third postoperative day. (The normal BUN for a rabbit in our laboratory is approximately 35 mg%.) Following unilateral nephrectomy, it will rise 10–15 mg% for an indefinite period before gradually falling to normal. If the transplant were technically unsuccessful, the recipient's BUN rose to greater than 100 mg% by the third postoperative day. Such rabbits were eliminated from the experiment.

The BUN for each rabbit was determined daily. Onset of rejection was defined as that day on which the BUN increased by 25% or more over the value obtained on the third postoperative day. After the initial rise in BUN, uremia always increased rapidly until the death of the animal. On most rabbits a biopsy of the transplanted kidney was obtained at the time of rejection. Hyperacute rejection, when it occurred, was diagnosed by gross and microscopic examination of the kidney.

Experimental Design

Five groups of NZW rabbits received renal allografts from Dutch rabbit donors.

Group I—Control Rabbits

Thirteen rabbits received a renal allograft without further treatment.

Group II—Actively Immunized Rabbits

Eight rabbits, each immunized against a donor rabbit according to the same protocol used to prepare donor specific alloantibody, received a renal allograft from the donor rabbit against which they had developed specific lymphocytotoxic antibody.

Group III—Rabbits Passively Immunized with Donor Specific Alloantibody.

Nine rabbits received a renal allograft followed by immediate infusion of 100 mg, or more, of IgG alloantibody that was raised in a third party rabbit specifically against the donor rabbit, and was demonstrably cytotoxic against the donor, but not recipient, lymphocytes.

Group IV—Rabbits Treated with Non-specific F(ab′)₂ Alloantibody Fragments

Four renal allograft recipients were treated immediately pretransplant and posttransplant, and then daily for one week, with intravenous injections of 100–500 mg of $F(ab')_2$ prepared from IgG alloantibody raised against a rabbit other than the donor. The alloantibody from which the $F(ab')_2$ was prepared had no cytotoxic activity against either the donor or recipient.

Group V—Rabbits Treated with Donor Specific F(ab′)₂ Alloantibody Fragments

Twelve renal allograft recipients were treated immediately before and after transplantation and then daily for 6–14 days (mean of 8.5 days) with intravenous injections of 100–500 mg of $F(ab')_2$ prepared from IgG cytotoxic alloantibody raised in a third party rabbit against the specific donor rabbit. Antiserum from which each donor specific $F(ab')_2$ alloantibody was derived was tested for lymphocytotoxic activity against a panel of NZW rabbits (Fig. 1). We selected as the recipient a rabbit whose lymphocytes were completely nonreactive with the donor specific antiserum. We tested 5–21 rabbits for each of the 12 donor specific alloantisera before we found one that met the above criteria. This method of selection assured us 1) that the donor rabbit possessed antigens absent in the recipient rabbit, and 2) that the donor specific alloantibody was directed against at least some, if not most or all, of the histocompatibility antigens present only in the donor.

Results

The onset of rejection and time of death following kidney transplantation are summarized for the five groups of rabbits in Table 1.

Group I

Untreated control rabbits rejected the allografted kidney 4–9 days following transplantation (mean rejection time 6.0 ± 0.4 [S.E.] days). Renal biopsies obtained at the onset of uremia showed diffuse mononuclear cell infiltration consistent with the rejection process. Biopsies taken at later intervals showed that the intensity of the infiltration increased with time.

Group II

Actively immunized rabbits showed both gross and microscopic evidence of hyperacute rejection, manifested either as an acute hemorrhagic infarction of the entire

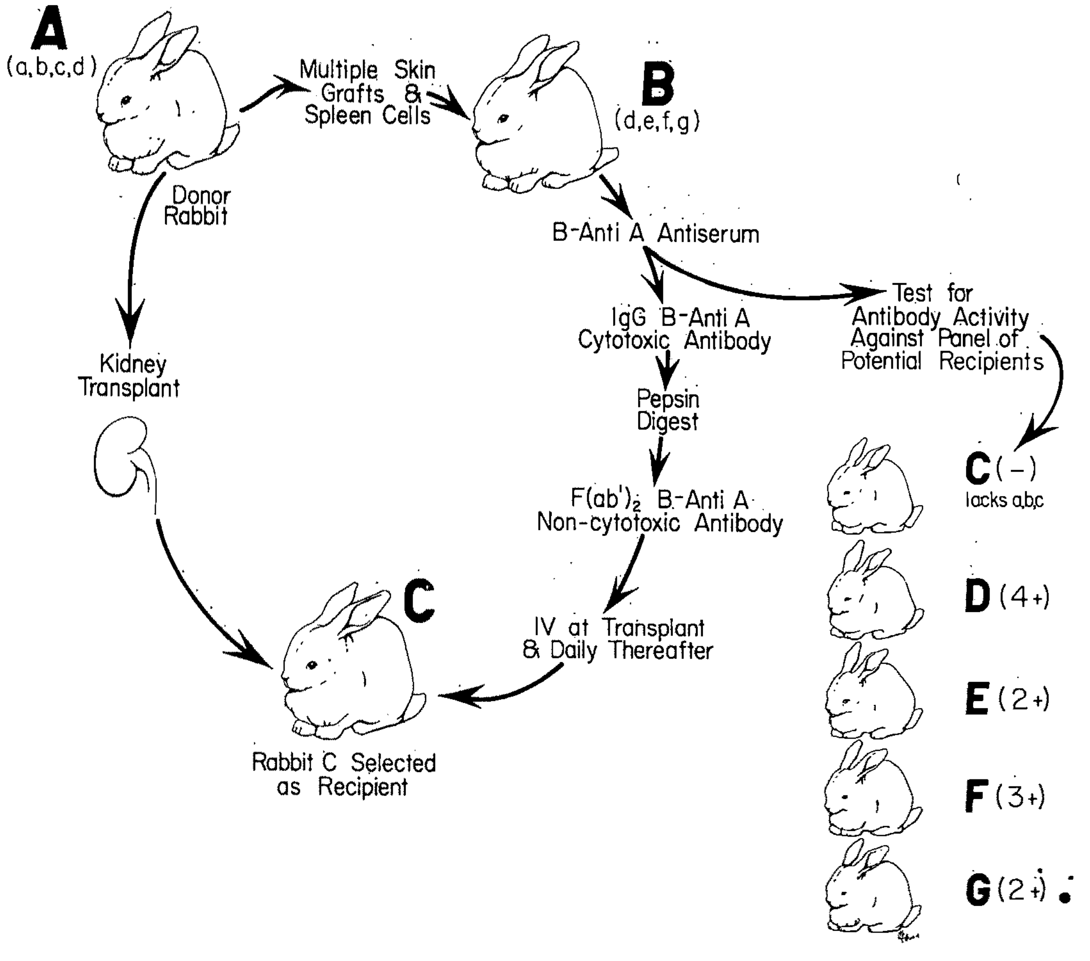
A
(a,b,c,d)
Multiple Skin Grafts & Spleen Cells
B
(d,e,f,g)
Donor Rabbit
B-Anti A Antiserum
Test for Antibody Activity Against Panel of Potential Recipients
IgG B-Anti A Cytotoxic Antibody
Pepsin Digest
F(ab')₂ B-Anti A Non-cytotoxic Antibody
IV at Transplant & Daily Thereafter
Kidney Transplant
C
Rabbit C Selected as Recipient
C(-) lacks a,b,c
D(4+)
E(2+)
F(3+)
G(2+)

FIG. 1. Experimental design. Antiserum against kidney donor rabbit (A) made in third party rabbit (B) is tested for lymphocytotoxic activity against a panel of potential recipient rabbits. A rabbit (C) against which there is no cross-reactivity is selected to be the recipient, assuring that the recipient rabbit lacks histocompatibility antigens present in the donor. Cytotoxic IgG obtained from the hyperimmune alloantisera is converted to non-cytotoxic donor specific $F(ab')_2$ alloantibody by pepsin digestion and administered daily to the recipient rabbit beginning on the day of transplantation.

TABLE 1. *Day of Rejection in Five Groups of Rabbits Receiving Renal Allografts*

Group I	Group II	Group III	Group IV	Group V		
13 Control Rabbits Untreated	8 Rabbits Actively Immunized	9 Rabbits Treated with Donor Specific IgG Alloantibody	4 Rabbits Treated with Non-specific $F(ab')_2$ Alloantibody	12 Rabbits Treated with Donor Specific $F(ab')_2$ Alloantibody	Daily Dose and Duration of $F(ab')_2$ Treatment†*	Interval in Days from Termination of $F(ab')_2$ Treatment to Rejection
6	<1	1	5	26	100 mg × 8 days	18
5	<1	<1	7	12	500 mg × 8 days	4
4	1	1	6	13	200 mg × 7 days	6
5	1	6	7	26	500 mg × 14 days	12
4	<1	1		10	100 mg × 10 days	0
5	1	4		13	100 mg × 7 days	6
6	<1	<1		25	500 mg × 6 days	19
8	<1	1		12	220 mg × 12 days	0
5		1		6	400 mg × 6 days	0
9				7	260 mg × 7 days	0
7				16	400 mg × 10 days	6
8				8	400 mg × 8 days	0
6						
Mean of 6.0 ± 0.4 (S.E.) Days	Hyperacute Rejection in All Rabbits	Hyperacute Rejection in 7/9 Rabbits	Mean of 6.2 ± 0.4 (S.E.) Days	Mean of 14.5 ± 2.1 (S.E.) Days†	*Double Dose Day of Transplant	Mean of 5.9 ± 2.0 (S.E.) Days

† $p < 0.001$ when compared with Group 1

kidney within a few hours of transplantation, or as an acute cortical necrosis evident within 24 hours, similar to that described by Klassen and Milgrom.[17] Animals in this group were killed after the hyperacute rejection was diagnosed.

Group III

Seven of the nine rabbits, after receiving donor specific IgG alloantibody, hyperacutely rejected the allografted kidney. Their lesions were similar to those seen in the actively immunized group. Two rabbits rejected the grafted kidney 4 and 6 days after transplantation.

Group IV

The four rabbits treated with non-specific $F(ab')_2$ alloantibody rejected their allografted kidneys 5–7 days (mean of 6.2 ± 0.4 [S.E.] days).

Group V

The onset of rejection varied considerably in the 13 rabbits treated with donor specific $F(ab')_2$ alloantibody. Their rejection episodes took place 6–26 days after transplantation (mean rejection time 14.5 ± 2.1 [S.E.] days). Prolongation of graft survival was statistically significant when compared to untreated control animals ($p < 0.001$ by Student's t-test). Five rabbits rejected the grafted kidney while still receiving daily $F(ab')_2$ injections 6, 7, 8, 10, and 12 days after transplantation; their rejection was delayed only minimally if at all. In the other seven animals, rejection did not begin until after $F(ab')_2$ administration had been discontinued. Four of these seven rabbits received $F(ab')_2$ for 8, 7, 7, and 10 days and rejected the allografted kidney at 12, 13, 13 and 16 days after transplantation; there were intervals of 4, 6, 6, and 6 days, respectively between the termination of $F(ab')_2$ treatment and onset of rejection. The other three rabbits received $F(ab')_2$ for 8, 14, and 6 days, and their onset of rejection was greatly delayed to 26, 26, and 25 days after transplantation; in these rabbits, the intervals between termination of treatment and rejection were 18, 12, and 19 days. Histological examination of renal biopsies performed at the time of BUN rise confirmed the presence of a cellular rejection process.

Discussion

We prolonged renal allograft survival in rabbits through the systemic administration of $F(ab')_2$ antibody fragments derived from cytotoxic IgG alloantibody directed against donor antigens that is capable of mediating hyperacute rejection in the unmodified state.

We chose the rabbit as a model for the induction of passive immunological enhancement of renal allografts because: 1) the current model of immunological enhancement in the rat has little pertinent clinical significance (the rat kidney is resistant to hyperacute rejection); 2) the allografted rabbit kidney is susceptible to antibody mediated hyperacute rejection; and 3) although larger than a rat, rabbits are small laboratory animals, and are therefore economically and logistically advantageous for use. These reasons are similar to those expressed by Holter *et al.*[12] and McDowall *et al.*[21]

There are, however, both advantages and disadvantages of having to work with the outbred strains of rabbits. Alloantibody production must either be tailored for each donor-recipient pair, or it must be polyspecific enough to cover all possible donor-recipient combinations. On the other hand an outbred model simulates the clinical situation.

We were able to induce hyperacute rejection of renal allografts in rabbits, either by active immunization or with passive transfer of IgG alloantibody directed against donor antigens (Groups II & III). Renal allograft recipients treated with non-specific F(ab')$_2$ (Group IV) received no disconcernable benefit; they rejected their grafts at the same time as the untreated controls (Group I).

Donor specific F(ab')$_2$ alloantibody was successful in delaying rejection of an allografted kidney (Group V). Factors which may have contributed to this success include: 1) the utilization of F(ab')$_2$ derived from alloantisera obtained by hyperimmunization; 2) the administration of F(ab')$_2$ frequently and in large quantities; and 3) selection of recipients so that the F(ab')$_2$ alloantibody was directed against most or all of the antigens present only in the donor.

To increase the probability of producing high affinity antibodies we used multiple immunizations to raise donor specific alloantisera. High affinity antibodies are more efficient suppressors of a specific humoral immune response than are low affinity antibodies,[35] and the same correlation may well hold true for antibody mediated suppression of a cellular immune response.

Passively administered F(ab')$_2$ antibody can inhibit a specific humoral immune response,[7] but to be effective, it must be administered repeatedly because of its short half-life.[32] Sinclair[29] has demonstrated that F(ab')$_2$ antibody is a thousand fold less potent at suppressing a specific antibody response than is an equivalent amount of IgG, and it may be similarly inefficient at inhibiting a cellular immune reaction. For these reasons the recipient rabbits received relatively large quantities of donor specific F(ab')$_2$ alloantibody daily.

In some rabbits of Group V the rejection mechanism was not delayed at all, even though they were still receiving donor specific F(ab')$_2$ alloantibody. Perhaps in those cases the F(ab')$_2$ was not directed against a major histocompatibility mismatch between the donor and recipient, or was not administered in sufficient quantities. Larger and more frequent infusions of F(ab')$_2$ might also have been beneficial for those rabbits in which rejection was delayed but still occurred even while receiving F(ab')$_2$.

Over 50% of the renal allograft recipients in Group V showed no signs of rejection until several days after cessation of F(ab')$_2$ injections. Conceivably, rejection could have been permanently suppressed by continuous administration. In rodents however, repeated administration of enhancing antisera or its IgG fraction does not significantly prolong skin allograft survival over that achieved with a single injection.[27] At best in the rabbit the antigen specific immunosuppressive effect of passively infused donor specific F(ab')$_2$ is limited to the duration of its administration. Once F(ab')$_2$ infusion is discontinued, the rejection process will soon be initiated, if it is not already underway.

In the rat, immunological enhancement of a renal allograft can be induced by administration of unmodified donor specific alloantibody.[11,23,33] F(ab')$_2$ alloantibody has also been effective when administered directly into the renal artery of the graft.[28] In the rat, autoenhancement from the recipient's own humoral response against the graft probably accounts for the graft's continued survival after passively administered enhancing antibody has been dissipated.[11] As our results show, autoenhancement does not occur in the rabbit. In the rabbit a humoral immune response against donor antigens, even if capable of suppressing or blocking cell mediated immunity to the same antigens, would be detrimental in its own right to the graft.

The method we employed to choose a recipient rabbit for each specific renal allograft donor was also an important influence on our results. Selection of a recipient against which donor specific lymphocytotoxic alloantibody raised in a third party had no cytotoxic activity assured us that the recipient lacked antigens that were present in the donor, and that the F(ab')$_2$ fragments employed were directed against these disparities. Delay in rejection of the allografted kidney, therefore, could not be attributed to fortuitous histocompatibility matching.

This selection method, however, still allows the recipient to lack alloantigens shared by both the donor and the rabbit in which the donor specific alloantibody was produced. If these antigens are fortuitously present in the donor, the alloantibody fragments would be directed against some, but not all, antigens present only in the donor. The circumstance may have been present for those donor-recipient combinations of Group V when graft rejection was not delayed at all. To use alloantibody fragments raised in a third party, the third party should ideally lack all the transplantation antigens that are also absent in the recipient but present in the donor. Selection could most readily be achieved by complete tissue typing. One major histocompatibility locus (RL-A) has been identified in the rabbit by Tissot *et al.*,[34] but tissue typing of all individual antigens is not yet possible.

McDowall *et al.*[21] used a limited form of tissue typing in the rabbit to identify an alloantigen or group of segregating antigens that they termed alpha. They attempted to produce passive immunological enhancement of renal allografts transplanted from a rabbit possessing the alpha antigen group, to one that lacked the alpha antigen group. In these experiments whole antiserum directed against alpha alloantigen(s) was employed as the enhancing agent. Recipient survival was prolonged in some instances, but often was associated with a chronic rejection process. In addition, hyperacute rejection of the allograft occurred in some recipients. The results of McDowall *et al.*[21] indicate that use of unmodified donor specific antibody can prolong graft survival in some rabbits, but the effect is unpredictable and the risk of hyperacute rejection is considerable.

The use of F(ab')$_2$ alloantibody fragments at least obviates the occurrence of hyperacute rejection, and our experience indicates that graft rejection can be delayed in some instances with this treatment alone. Perhaps concomitant administration of small or suboptimal doses of immunosuppressive agents would have produced more positive results. Wilson *et al.*[37] have shown that antigen pretreatment of dog renal allograft recipients prolongs survival only if suboptimal doses of azathioprine are administered. In the dog, small doses of azathioprine also have an immunosuppressant effect synergistic with ALG.[5] Our attempts at producing immunological enhancement of dog renal allografts with donor specific F(ab')$_2$ have not been successful, even when it was used in conjunction with azathioprine.[6] Wren *et al.* did, however, achieve a prolongation of graft survival in dogs by using polyspecific F(ab')$_2$ and azathioprine.[38,39] We could not prolong renal allograft survival in the rabbit with F(ab')$_2$ derived from hyperimmune alloantibody not raised specifically against the donor animal (Group IV). However, the F(ab')$_2$ used in this group of rabbits definitely had no antibody activity against donor antigens, while the polyspecific F(ab')$_2$ utilized by Wren *et al.*[38,39] was active against the donor dog. Perhaps polyspecific F(ab')$_2$ could be successfully employed in the rabbit if prepared according to the protocol of Wilson's group,[38,39] and administered in conjunction with immunosuppressive drugs.

Conceptually, the use of F(ab')$_2$ antibody fragments to suppress a specific immune response is an appealing method of preventing graft rejection. Its major appeals are the elimination of hyperacute rejection associated with IgG antibody and the decreased need for, and risk of, generalized immunosuppression.

Clinical attempts to produce immunological enhancement by administration of donor specific F(ab')$_2$ alloantibody to recipients of living related kidney allografts have been reported.[4,11,31] French and Batchelor reported that grafts functioned satisfactory in some patients for several months with minimal doses of immunosuppressive agents.[11] It is impossible to say whether or not the F(ab')$_2$ infusion was the determining influence, and rejection episodes did eventually occur. Standard immunosuppressive treatment was also given in Solheim's one clinical case using F(ab')$_2$, but acute cell mediated rejection occurred in spite of its administration.[31]

Obviously much still remains to be learned about the influence that humoral and cellular immune mechanisms exert on each other. Using rats as his model, Parish showed[26] a definite relationship between the two mechanisms. During active immunization a heightened level of humoral immunity was associated with depressed cellular immunity, and vice versa. However, in his system using Flagella antigens, the passive administration of antibody suppressed a humoral immune response at the same time that it accentuated a cell mediated response, which is just the opposite of the effect necessary for immunological enhancement to occur.

Theories on immunological enhancement usually propose that immunological activity is altered as a result of either an afferent, central, or efferent blockade of a cellular immune response. Experimental evidence exists to support or refute a blockade occurring at any of these levels,[9] and the exact mechanisms remain in doubt. In the experiment reported here, some rabbits treated with donor specific F(ab')$_2$ alloantibody did not reject their renal allografts until several days after F(ab')$_2$ administration was discontinued. These results are compatible with either a peripheral or central blockade theory. Any further discussion of mechanisms must remain speculative.

We must learn more about the biological activity of the various portions of the immunoglobulin molecule if we are to properly use antibody fragments for induction of passive immunological enhancement. Removal of the Fc fragment is important in order to prevent the undesirable function of complement fixation, but at the same time other desirable functions of the Fc portion of immunoglobulin may be obviated. The Fc fragment, by regulating the level of an immune response,[30] may be of importance in those systems where immunological enhancement is mediated through IgG. The effect that pepsin digestion will have on noncytotoxic IgG blocking factors, shown to appear in man following renal transplantation,[22] should also be determined. Catabolism of IgG is also related to the Fc fragment.[32] The short half-life of F(ab')$_2$ when compared to IgG is a major obstacle to the use of passive immunological enhancement, even if F(ab')$_2$ is able to mediate this effect without the presence of the Fc fragment.

The technique of passive immunological enhancement does have potential clinical application. Planned immunizations of family members could be used to produce alloantisera suitable for pepsin digestion and use in living related renal allograft recipients. Alternatively, if HL-A typing sera could be made available in large quantities, alloantisera selected for reactivity against antigens present in the donor but absent in the recipient could be pooled as a potential source for production of immunosuppressing alloantibody fragments. Our experiment emphasizes the favorable effect and also the logistic difficulties that may be encountered when attempting to delay rejection with donor specific F(ab')$_2$ alloantibody fragments in an outbred species susceptible to hyperacute rejection.

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Giant Sigmoid Diverticula:

A Review

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Two patients with giant sigmoid diverticula are added to 13 cases reported in the literature and the clinical features of this rare complication of diverticulosis are reviewed. These lesions probably arise as pseudodiverticula of the sigmoid colon with herniation of the mucosa through the muscle wall. They become progressively inflated by colonic gas via a ball-valve type mechanism. They are best treated by resection of the diverticulum, in continuity with the involved sigmoid, and primary anastomosis.

DIVERTICULOSIS OF THE COLON is a common clinical entity. Its incidence on barium enema or at necropsy rises with increasing age so that, at age 65, it is found in at least 35% of individuals studied. Most frequently, it comes to the surgeon's attention because of one of its complications, i.e. abdominal pain, lower GI bleeding, perforation, fistula or intestinal obstruction. A much rarer manifestation, however, is the formation of a giant diverticulum. In 1953, Hughes and Greene[6] first reported the case of a "solitary air cyst" arising from the antimesenteric border of the sigmoid colon. Since that time, approximately a dozen isolated case reports have appeared in the literature variously termed "giant gas cyst," "giant sigmoid diverticulum," or "intestinal gas cyst." Our own recent experience with two such cases stimulated a review of the literature on this subject. It is the purpose of this paper to summarize the clinical and diagnostic features of this distinct entity and to comment on its etiology and therapy.

Case Reports

Case 1. (H.S.). This 70-year-old white male presented with a two-day history of steady, dull epigastric pain of increasing severity without radiation or associated nausea and vomiting. The patient had not moved his bowels for the past two days, but had not otherwise noted any recent change in bowel movement. He denied any previous history of abdominal distress. Past medical history and review of systems were otherwise unremarkable. Physical examination revealed an afebrile, elderly white male in no acute distress. His abdomen was distended with a large, tympanitic, tender, fixed, epigastric mass. A nasogastric tube was passed but failed to deflate the cyst. Aspiration of the fluid from the stomach revealed it to be guaiac negative as was his stool. Sigmoidoscopy was performed to 25 cm and was unremarkable. White blood count on admission was 19,900 with a shift to the left. Vandenberg and amylase were within normal limits. Plain film of the abdomen revealed a large, round, air-filled cyst in the epigastrium and a smaller gas collection in the lower abdomen (Fig. 1). Barium enema and upper GI series failed to demonstrate any communication with the cyst and the patient was taken to the operating room. At operation, two large gas-filled cysts were found located on the antimesenteric border of the sigmoid colon (Fig. 2). They were adherent to the transverse mesocolon and overlying omentum, but were readily separable. The cysts could not be deflated manually. A resection of approximately 20 cm of sigmoid in continuity with the two large cysts was performed with a primary anastomosis. Protecting colostomy was not performed. Postoperatively the patient's course was uncomplicated and he left the hospital ten days later.

Case 2. (N.D.). This 78-year-old Italian-born white female was admitted because of recurrent tachycardia and chest pains on a background of coronary insufficiency. While in the hospital she developed abdominal pain which became progressively more severe and was associated with an increasing fullness in her abdomen. Plain film of the abdomen revealed a large gas-filled structure in the right, lower quadrant. Barium enema was performed and demonstrated this to be a diverticulum of the sigmoid colon communicating with the lumen (Fig. 3). The patient was taken to the operating room where a huge diverticulum of the sigmoid colon was identified. It could be emptied easily at operation into the lumen and had areas of erythema and injection suggesting either a partial infarction or localized perforation. The lower portion of the diverticulum was densely adherent to the uterus and the pelvis on the right side. The diverticulum was dissected until its neck could be identified and was resected at this point. The opening in the sigmoid was then closed in a two-layer fashion. A protecting right transverse colostomy was performed. Postoperatively, except for a minor wound infection, the patient's course was generally benign and she was discharged three weeks later.

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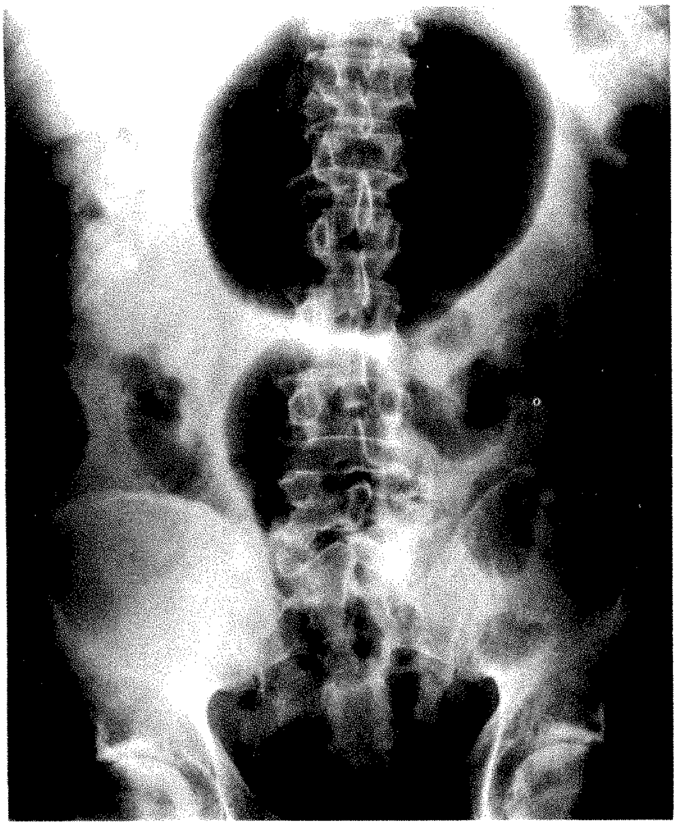

FIG. 1. Plain abdominal roentgenogram (Case 1.) showing a smooth rounded gas collection overlying the mid-epigastrium and a smaller vertically elongated collection over the lumbosacral region.

Discussion

The patients with giant sigmoid diverticula present a remarkably uniform clinical picture (Table 1). They are generally elderly, with an average age of 62 years, and are equally distributed as to sex. They most frequently complain of vague abdominal pain and the presence of an enlarging abdominal mass which on physical examination is generally movable and tympanitic but may or may not be tender. If the cyst has expanded acutely, they may show all the signs of an acute inflammatory reaction with leukocytosis as high as 25,000 and fever. Plain films of the abdomen demonstrate a large (13 cm on the average) generally solitary, anteriorly placed, gas-filled cyst usually closely associated with the sigmoid colon and displacing various normal intra-abdominal structures. The barium enema examination uniformly discloses the presence of associated diverticulosis but will fill the diverticulum in only about a third of the patients studied. Sigmoidoscopy, when performed, has been uniformly non-contributory.

The presence of a large gas-filled cyst in the abdomen raises numerous diagnostic considerations (Table 2). The gallbladder may occasionally contain large amounts of air. This is most commonly secondary to a fistulous communication with the GI tract due either to a perforating gallstone or peptic ulcer. In either case, the gallbladder rarely attains the size of these diverticula and the presence of air in the biliary tree, as well as the precedent history of characteristic abdominal distress serve to differentiate these conditions. Less commonly, gas forming organisms may infect the gallbladder wall resulting in emphysematous cholecystitis, a

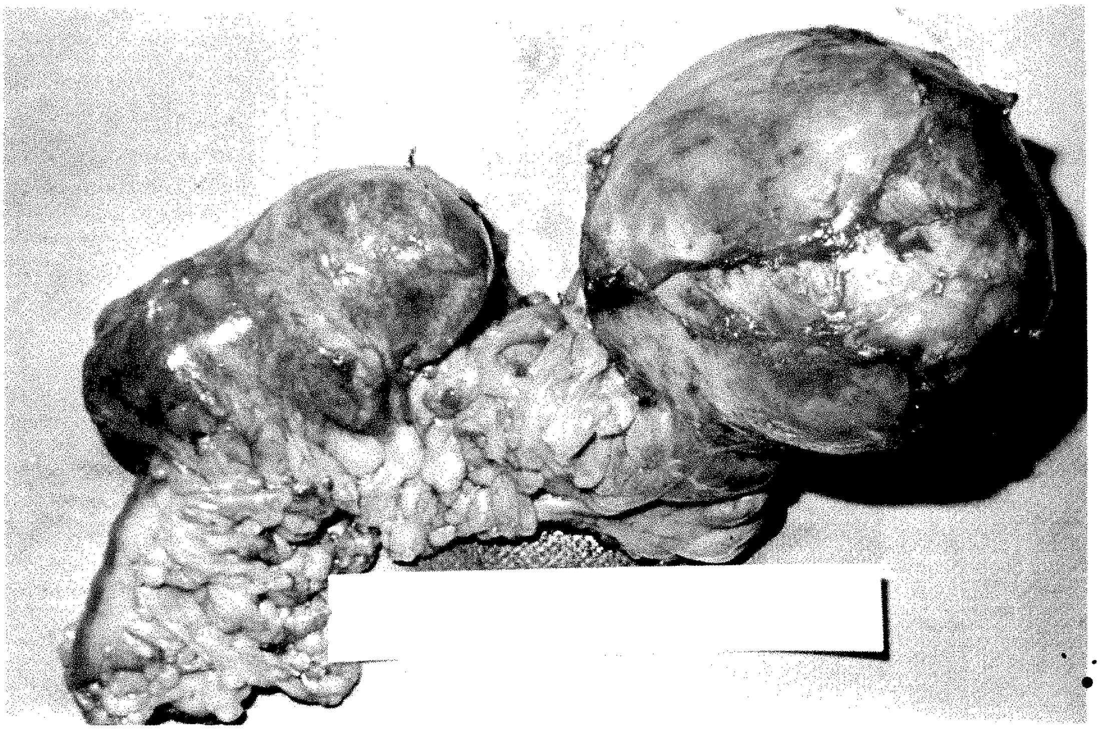

FIG. 2. Resection specimen (Case 1.) showing a 20 cm segment of sigmoid colon with two cystic structures projecting from the anti-mesenteric border. Associated diverticular disease is visible.

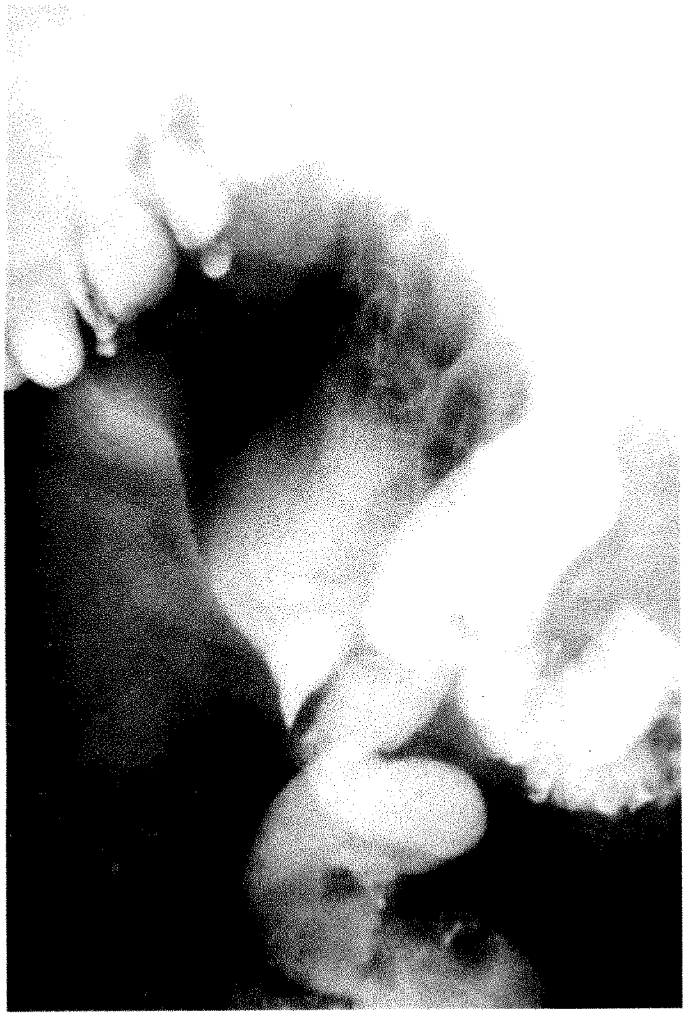

FIG. 3. Barium enema angle view of the sigmoid (Case 2.) showing barium entering cyst through a narrow funnel-like neck.

TABLE 1. *Summary of Clinical Features in Total Collected Cases*

Number of Patients	15 (7 female, 8 male)
Average Age	62 ± 20
Chief Complaint	
Abdominal pain	73%
Abdominal mass	50%
Size of Cyst	13 cm ± 7 cm
Communication with Lumen	
Anatomic	66%
Demonstrated on BaE	33%
Associated Diverticulosis	100%
Operative Therapy	
Sigmoid resection	75%
Diverticulectomy alone	25%

disease usually seen in the elderly diabetics. This is an acute prostrating illness associated with marked fever, leukocytosis, and right upper quadrant tenderness. These patients are considerably more toxic and a large, movable cystic structure such as we see in the patients with giant sigmoid diverticula is not in keeping with the findings of emphysematous cholecystitis.

Rarely a Meckel's diverticulum may become quite large and cystic and present as an ovoid or irregular air-filled structure on x-ray.[7] These patients are generally much younger and the cyst is always attached to the terminal ileum rather than the sigmoid. Similarly, jejuno-ileal diverticula, other than Meckel's may become distended although generally to a lesser degree and mimic giant sigmoid diverticula. Upper GI series with small bowel follow-through might be helpful in excluding this group of individuals. Intestinal duplications can communicate with the bowel lumen and may become cystically dilated, assuming an appearance quite similar to that of giant sigmoid diverticular. Although presented by these authors as examples of giant sigmoid diverticula, the presence of smooth muscle bundles in the cyst wall suggest that perhaps this was the situation in three of the cases reported here.[6,10,12] Generally, however, duplications occur along the mesenteric border between the leaves of the mesentery, are tubular, lack communication with the lumen, and are found in much younger patients. In addition, while such lesions can occur in the sigmoid, they are extremely rare in this location, being commonest in the ileum.

Although the question of pneumatosis cystoides intestinalis frequently arises whenever gas-filled cysts are encountered on plain film of the abdomen, they are always multiple and much smaller in size, and should not be confused with this entity.

The urinary bladder, like the gallbladder, may become distended with air. The usual cause of this gas is a fistulous communication with bowel or infection with gas forming organisms. However, the gas is readily and characteristically voided by the patient and is rarely noted on x-ray.

Abscesses may contain large amounts of air whenever gas-forming organisms are present. However, their lack of mobility, smaller size, and associated clinical signs of sepsis should readily differentiate this condition.

Occasionally, pancreatic pseudocysts may become suprainfected with gas-forming organisms. However, their

TABLE 2. *Differential Diagnosis of Large Abdominal Gas-filled Cysts*

- Gallbladder
  - Cholecyst-enteric fistula
  - Emphysematous cholecystitis
- Small Intestine
  - Meckel's diverticulum
  - Jejuno-ileal diverticula
  - Duplications
- Pnematosis Cystoides Intestinalis
- Urinary Bladder
  - Vesico-enteric fistula
  - Emphysematous cystitis
- Abscesses
  - Superinfected pancreatic pseudocysts
- Colon
  - Volvulus of cecum or sigmoid
  - Duplication
  - Sigmoid diverticula

retroperitoneal location in the lesser sac and associated pancreatitis are usually pathognomonic.

Volvulus of the cecum or sigmoid colon can often result in gas-filled structures of impressive size on plain film of the abdomen. In most cases, the associated bowel obstruction, the preoperative contrast studies, and the antecedent history would make diagnosis fairly obvious.

Two principal theories have been advanced as to the etiology of these giant diverticula:[3]

1. They represent a pseudodiverticulum of mucosa and submucosa through muscularis whose communication with the bowel lumen becomes so narrowed by inflammation that a ball-valve mechanism is created whereby gas can enter the cyst as intraluminal pressure increases but cannot exit.

2. Gas forming organisms within the cyst produce progressive distention once its stalk becomes obliterated.

We favor the "ball-valve theory" for several reasons. Anatomic communication is demonstrable in over two-thirds of the cases, making it difficult to believe that gas formed by microorganisms in the cyst would not vent into the lumen. Secondly, in at least one case,[1] the fluid aspirated from the cyst failed to grow any organisms on culture. Lastly, the remarkable case of Frankenfeld[5] in which the cyst waxed and waned in sized and dramatically recurred as the patient strained at stool is most suggestive of a ball-valve type mechanism.

At operation all but one[2] of these diverticula were found to originate from the anti-mesenteric border of the sigmoid colon. Although generally adherent to omentum and transverse colon, they were easily separable and had a distinct wall of their own. In some cases,[5] the cyst could be deflated manually prior to resection. In one of our own cases, H.S., and in three of the cases reported in the literature,[10,12,13] the sigmoid contained at least two distinct giant diverticula.

If we exclude those cases which demonstrated mucosa lining the cyst and smooth muscle bundles in the wall as representing communicating intestinal duplications,[6,10,12] pathologically the cysts were remarkably similar. No definite mucosa was identified. Instead, they were lined by pale, shiny membranes composed of a very vascular, dense fibrous tissue heavily infiltrated by chronic inflammatory cells and foreign body giant cells. The smooth muscle bundles of the sigmoid ended abruptly at the neck of the divertuculum and no real muscle bundles could be identified in the walls of the cysts themselves.

In view of these findings we feel certain that the vast majority of these arise as pseudodiverticula of colonic mucosa and enlarge progressively because of inflation by colonic gases trapped within the cyst via a ball-valve type mechanism. Either because of the marked inflammatory reaction present in the wall, or, less likely, because of the pressure of the trapped gas, the mucosa undergoes degeneration leaving a wall composed solely of dense inflammatory tissue. We find no evidence to support the hypothesis that these cysts represent localized perforation of the sigmoid which become progressively enlarged by extruded gas. They are readily separable from adjacent structures and have a distinct wall of their own. One can find a complete spectrum of lesions ranging from typical sigmoid diverticula, 1–2 cm in size, to the giant lesions which we have discussed thus further suggesting their origin.

As described by Frankenfeld,[5] these cysts can undergo torsion and become symptomatic or as noted in one of our own cases, M.D., the wall can undergo focal infarction or perforation. For this reason we feel they are best managed surgically. Although resection of the cyst alone was performed in 25% of the cases, we believe that in view of the wide mouth occasionally found in some of these diverticula, as well as inflammation in the adjacent bowel wall, resection of the diverticulum in continuity with the involved sigmoid is the preferred mode of therapy. Primary anastomoses have uniformly been performed and protecting colostomy has rarely been empolyed.

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Clinical Application of Cytochrome $a(+a_3)$ Assay of Mitochondria from Liver Specimens:

An Aid in Determining Metabolic Tolerance of Liver Remnant for Hepatic Resection

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Measurement of cytochrome $a(+a_3)$ contents in liver mitochondria was made on 52 biopsy specimens of patients with liver tumor. Patients having higher cytochrome $a(+a_3)$ contents in mitochondria from remaining liver than those of normal human liver mitochondria could survive well major liver resections whether or not associated with liver cirrhosis. However, patients with cytochrome $a(+a_3)$ contents less than 0.5×10^{-10} moles per mg protein showed a high rate of postoperative complication (80%) and death (40%) in spite of minor operation. In routinely used liver function tests such as serum albumin, A/G ratio, SGOT, total bilirubin, prothrombin time, BSP and TTT, there were no significant differences between patients with cytochrome $a(+a_3)$ contents more than 0.5×10^{-10} moles per mg protein and those less than 0.5. The results indicate that routine laboratory studies do not have much diagnostic value in estimation of a marked decrease of mitochondrial cytochrome $a(+a_3)$ contents. It is suggested that the measurements of cytochrome $a(+a_3)$ of the remnant liver should be done prior to a contemplated major resection.

MAJOR HEPATIC RESECTION is an accepted technique for treatment of liver cancer, but demands a precise knowledge of the alterations in metabolic and physiologic functions following major resection of functioning liver. Although directly related to the massiveness of liver resection, the risk of liver resection is relatively low in patients with normal remaining liver. When liver function is compromised with associated cirrhosis, however, the risk of operation is significantly increased. Several workers[2,4,14–16] have sought a reliable method for assessment of operative risk by comparing hepatic insufficiency following major hepatectomy with preoperative or postoperative liver function tests. However, there is at present no available method to predict hepatic failure that may result from the excision of large amounts of functioning liver. Therefore, it is of great importance to find the best way of judging the capacity of the liver remnant to enable the patient to survive a major hepatic resection.

Unpublished, as well as published, evidence has been obtained in recent years by us, suggesting that an enhancement of phosphorylative capacity of mitochondria is requisite for regenerating processes such as the synthesis of nuclear DNA and that metabolism of liver mitochondria is regulated by a mitochondria-stimulating factor in portal blood and enhanced with a rise in the portal factor available to viable mitochondria.[1,6,8,12] However, when the respiratory carriers—especially cytochrome $a(+a_3)$—of liver mitochondria are critically reduced, the phosphorylative capacities of mitochondria could not be significantly enhanced despite the presence of the portal factor.[12] Such a decrease of cytochrome

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a(+a_3) develops substantially with the progressive deterioration of clinical status of patients.[9] Measurements of cytochrome a(+a_3) contents of mitochondria from liver specimens have been proved to be useful in evaluating the hepatic functional reserve. In addition, it has been found that there is a definite relationship between the grade of liver mitochondrial derangement and the distribution of cancer in the liver.[10] As a consequence of those results, it has been suggested that it may be possible to predict which patients are most likely to have postoperative hepatic insufficiency following major hepatic resection.

The purpose of this study is to establish new or additional guideposts in evaluation of the ability of the remnant of liver tissue to adapt itself to postoperative functional demands. In this study, evidence will be presented that, when the contents of cytochrome a(+a_3) in mitochondria from the remnant liver are within normal limits or more, major hepatic resection could be successfully performed even in cirrhotic liver, while patients with a(+a_3) contents less than 0.5×10^{-10} moles per mg protein often could not tolerate even a minor operation.

Materials and Methods

Human biopsy material weighing 0.4–1.5 g from areas of the liver edge was obtained at operation, as reported previously.[7] A biochemical analysis of mitochondrial metabolism was made on 52 biopsy specimens of liver with primary and secondary tumors obtained immediately after laparotomy. Seventeen patients had primary tumors of the liver. All the other patients had secondary tumors: from the stomach in 23, the colon and rectum in 5, the pancreas in 6, and the gallbladder in 1. The ages of the patients ranged from 8 months to 72 years, with a mean of 56 years. There were 36 men and 16 women. Among them 12 patients have undergone liver resection for cancer, including three extended right hepatectomies. For comparison, 19 patients 14 to 47 aged (10 males, 9 females) who had clinically normal liver function and histologically normal findings of biopsy specimens were selected as controls, after receiving informed consent.

Isolation of Liver Mitochondria and Measurement of Respiratory Enzymes. Liver mitochondria were prepared by the method of Ozawa *et al.*[7] In the liver with multiple tumor nodules, approximately 0.2 mm thick slices of biopsy specimen were cut with a slicer (Natume, Co. Ltd.) and hepatic tissues were carefully separated by dissection from tumor tissues. The spectrophotometric techniques for the assay of cytochrome a(+a_3) contents are described elsewhere.[7] Protein was determined by the method of Lowry *et al.*[3] with crystalline bovine serum albumin as standard.

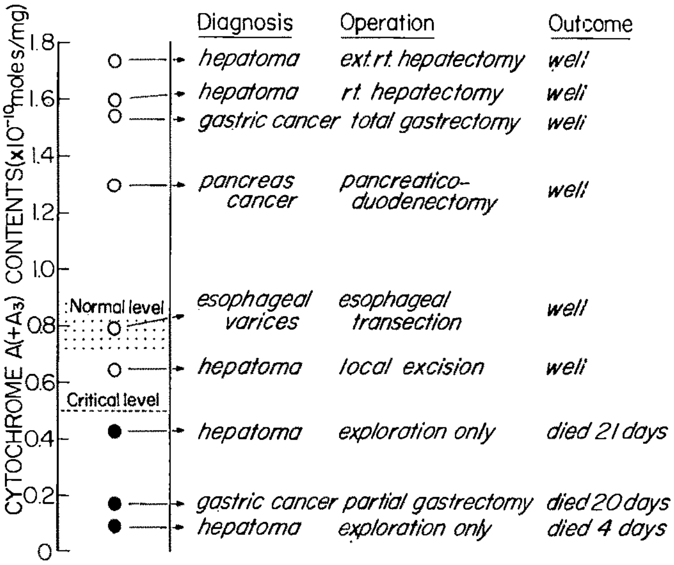


FIG. 1. Primary disease, type of surgery and cytochrome a(+a_3) contents in patients with liver cirrhosis. Laennec's cirrhosis in 8 patients except 1 patient of biliary cirrhosis (pancreas cancer).

Results

Table 1 shows the primary disease, type of surgery and contents of mitochondrial cytochrome a(+a_3) in 12 patients subjected to liver resection. The nature of the operative procedures varied in magnitude from local excision to extended right hepatectomy. The cytochrome a(+a_3) content of the mitochondria from the remaining liver varied widely from 0.5 to 1.7×10^{-10} moles per mg of mitochondrial protein. When the contents of cytochrome a(+a_3) in the mitochondria from remaining liver were within normal limits (0.81 ± 0.02 (mean ± S.E.) $\times 10^{-10}$ moles per mg protein)[7] or more, the 11 patients could survive major liver resection well. However, in a patient with cytochrome a(+a_3) contents of 0.5×10^{-10} moles per mg protein in mitochondria from the remaining liver (Pt. No. 9 in Table 1), marked jaundice and ascites rapidly developed postoperatively.

Table 2 shows the primary disease and type of surgery in 5 patients with operatively resectable cancer but a marked decrease in cytochrome a(+a_3) contents of mitochondria from the remaining liver. Although the preoperative assessment from routine liver function tests suggested that an adequate functional reserve was present, examinations of the liver biopsy materials revealed the mitochondrial derangement to be much more extensive than had been suspected. Therefore, although hepatic tumor was localized to one lobe, hepatic resections could not be performed. However, such patients showed a high rate of postoperative complication (80%) and death (40%) even if the operation were comparatively minor such as exploratory laparotomy and cholecystectomy. On the other hand, Table 3 shows the pri-

TABLE 1—Clinical Data in Patients With Resectable Cancer

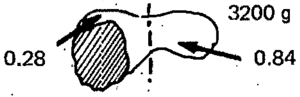
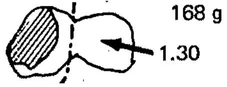
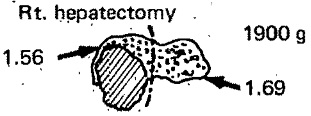
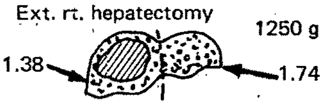
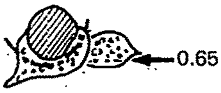
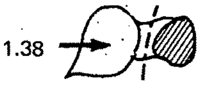
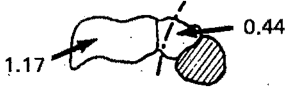
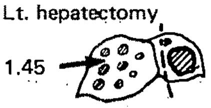
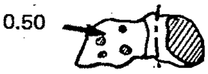
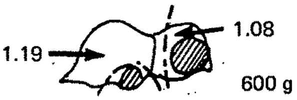
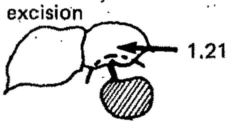
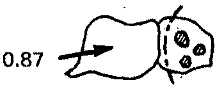
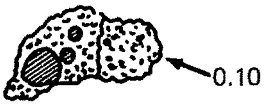
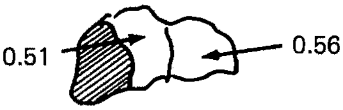
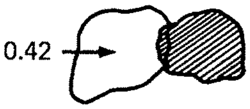
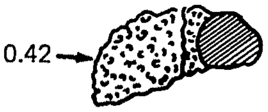
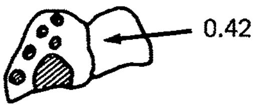
Pt. No.	Age Sex	Primary disease	Operation, Cytochrome a(+a3) content (10^{-10}moles/mg)	Associated cirrhosis	Postoperative course
1	27 M	Hepatoma	Ext. rt. hepatectomy  	(–)	well
2	0.8 M	Hepatoblastoma	Ext. rt. hepatectomy  	(–)	well
3	52 M	Hepatoma	Rt. hepatectomy  	Laennec's cirrhosis	well
4	52 F	Hepatoma	Ext. rt. hepatectomy  	Laennec's cirrhosis	Transient jaundice developed postoperatively
5	68 F	Hepatoma	Local excision  	Laennec's cirrhosis	well
6	45 M	Hepatoma	Lt. hepatectomy  	(–)	well
7	53 F	Hepatoma	Lt. hepatectomy  	(–)	well
8	59 M	Hepatoma	Lt. hepatectomy  	(–)	well
9	56 M	Gastric cancer with liver metastasis	Lt. hepatectomy+partial gastrectomy  	(–)	Marked jaundice and ascites developed
10	63 M	Gastric cancer with liver metastasis	Lt. hepatectomy+local excision  	(–)	well
11	1.3 M	Hamartoma	Local excision  	(–)	well
12	67 M	Gastric cancer with liver metastasis	Lt. hepatectomy+total gastrectomy  	(–)	well

TABLE 2—Clinical Data in Patients With Operatively Resectable Cancer and Marked Decrease of Cytochrome a(+a3) Contents of Liver Mitochondria

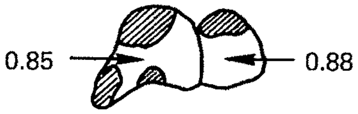
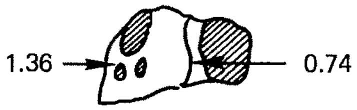
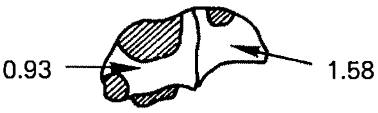
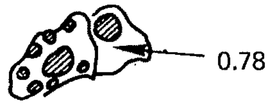
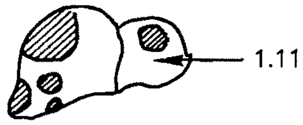
Pt. No.	Age Sex	Primary disease	Operation Cytochrome a(+a3) content (10^{-10}moles/mg)	Associated cirrhosis	Postoperative course
1	53 F	Hepatoma	Exploration only  0.10	Laennec's cirrhosis	died on fourth postoperative day
2	69 F	Hepatoma	Exploration only  0.51 0.56	–	Ascites developed before 10 days postoperatively
3	72 F	Cholangiocarcinoma	Ligation of the left portal vein  0.42	–	alive 8 months
4	48 M	Hepatoma	Exploration only  0.42	Laennec's cirrhosis	died on twenty-first postoperative day
5	47 F	Gastric cancer with liver metastasis	Cholecystectomy+T–tube drainage  0.42	–	Jaundice and marked of SGOT and alk. phos. continued over 1 month

mary disease and type of surgery in 5 patients with operatively unresectable cancer but mitochondrial cytochrome a(+a₃) contents more than normal. These patients fared relatively better than those with marked decrease of cytochrome a(+a₃) contents. In the remaining 30 patients, 60% or more of the liver was pervaded with tumor of multiple nodules and the contents of cytochrome a(+a₃) of liver mitochondria were less than 0.5 × 10^{-10} moles per mg protein. The patients with such heavy involvement due to cancer had the shortest survival following laparotomy.

Cirrhosis, often associated with hepatoma, was always considered a limiting factor for major massive resection because of the diffuse parenchymal lesions and general impairment in liver function. In the 9 patients with liver cirrhosis analyzed to date, 8 patients had Laennec's cirrhosis and 1 biliary cirrhosis with pancreas cancer. The contents of mitochondrial cytochrome a(+a₃) in those patients were widely distributed from 0.1 to 1.7 × 10^{-10} moles per mg protein (Fig. 1). Among them, 6 patients with cytochrome a(+a₃) contents more than normal could tolerate major operation well, while 3 patients with cytochrome a(+a₃) contents less than 0.5 × 10^{-10} moles per mg protein died within 21 days after exploratory laparotomy or partial gastrectomy. Thus, despite the presence or absence of cirrhosis, the fragility of patients with cytochrome a(+a₃) contents less than 0.5 × 10^{-10} moles per mg protein seemed endangered by a major operation.

Figure 2 shows the relationship between the laboratory findings just prior to operation and cytochrome a(+a₃) contents of liver mitochondria in 52 patients with liver tumor. In serum albumin, serum glutamic oxalacetic transaminase (SGOT), total bilirubin, prothrombin time, bromsulphalein test (BSP) and thymol turbidity test (TTT), there were no significant differences between patients having cytochrome a(+a₃) contents more than 0.5 × 10^{-10} moles per mg protein and those less than 0.5. Thus, routine laboratory studies are considered of little diagnostic value for accurate prediction of a marked

TABLE 3—Clinical Data in Patients With Operatively Unresectable Cancer and Cytochrome a(+a3) Contents more than Normal in Liver Mitochondria

Pt. No.	Age Sex	Primary disease	Operation Cytochrome a(+a3) content (10^{-10} moles/mg)	Associated cirrhosis	Postoperative course
1	57 M	Cholangio-carcinoma	Exploration only 	–	died 3 months post-operatively
2	43 M	Hepatoma	Ligation of the left portal vein 	–	died 5 months post-operatively
3	61 M	Hepatoma	Exploration only 	–	good 3 months post-operatively
4	44 F	Hepatoma	Ligation of the right hepatic artery 	–	died 2 months post-operatively
5	70 M	Hepatoma	Exploration only 	–	died 4 months post-operatively

decrease in mitochondrial cytochrome a(+a_3) contents and operative risk in individual patients with impaired liver function. On the other hand, in the postoperative level of serum albumin, there was a marked difference between above described two groups. In most of the patients with cytochrome a(+a_3) contents less than 0.5 × 10^{-10} moles per mg protein the serum albumin level decreased below 3 gm% even as early as 3 weeks following operation (Fig. 3). These indicate that in patients with cytochrome a(+a_3) contents less than 0.5 × 10^{-10} moles per mg protein, the synthesis of serum albumin is barely maintained at normal level prior to operation but is inhibited even with a relatively slight metabolic load such as exploratory laparotomy. Since the liver is

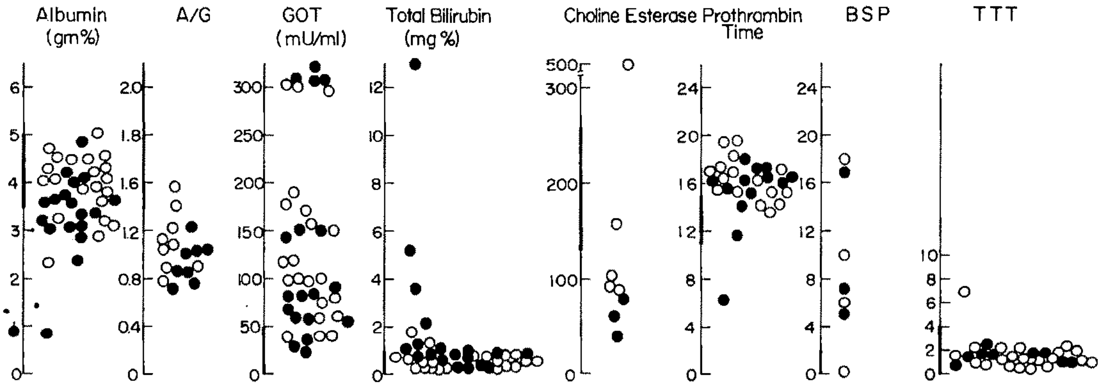


FIG. 2. Comparison of laboratory findings just prior to operation in patients with cytochrome a(+a_3) contents more than 0.5 × 10^{-10} per mg protein and those less than 0.5. ○—patients with cytochrome a(+a_3) contents more than 0.5 × 10^{-10} moles per mg protein. ●—patients with cytochrome a(+a_3) contents less than 0.5 × 10^{-10} moles per mg protein.

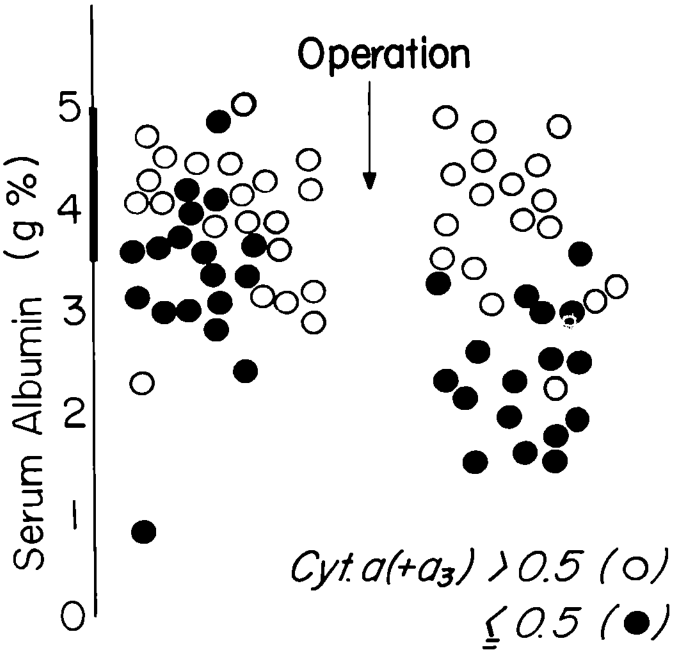


FIG. 3. Preoperative and postoperative level of serum albumin in patients with liver cancer. ○—patients with cytochrome a(+a$_3$) contents more than 0.5 × 10^{-10} moles per mg protein. ●—patients with cytochrome a(+a$_3$) contents less than 0.5 × 10^{-10} moles per mg protein.

the main manufacturer of albumin, a low albumin in these patients should be considered indicative of impaired hepatocellular function. Thus, considering that such progressive fall in serum albumin following operation was more frequently seen in patients with the content of cytochrome a(+a$_3$) less than 0.5 × 10^{-10} moles per mg protein, a marked decrease of the content of cytochrome a(+a$_3$) would provide a predictive information for avoiding operation in patients with seriously compromised liver function. In addition, in all patients with liver cancer in whom ascites was found at the time of operation the contents of cytochrome a(+a$_3$) was less than those of normal human liver mitochondria (Fig. 4). As ascites is a poor prognostic sign, the results also indicate the usefulness of cytochrome a(+a$_3$) assay.

On the other hand, an increase of respiratory enzymes results in a rise in over-all respiratory and phosphorylative capacities of liver and may be most favorable for the liver metabolism despite extensive liver damage. However, when the contents of cytochrome a(+a$_3$) in the mitochondria from the tumor-bearing lobe are remarkably increased, major hepatic resection must be avoided. The examples follow.

Case Reports

Case 1. A 52-year-old woman entered this hospital because of a huge mass in the right side of the abdomen. After preliminary diagnostic studies, extended right lobectomy (resection of 80% of liver containing functional liver tissues with cytochrome a(+a$_3$) contents more than 1.5 × 10^{-10} moles per mg protein) was carried out (Fig. 5, right). The pathological report on the operative specimen showed Laennec's cirrhosis. Within a few days following operation the patient began to show a progressive fall in serum albumin level and a marked increase of serum bilirubin level.

Case 2. A 52-year-old man was referred to this hospital with a huge mass in the right side of the abdomen. After preliminary diagnostic studies a resection of right lobe was carried out. The operative specimen showed Laennec's cirrhosis. The mitochondria from the liver specimen showed the contents of cytochrome a(+a$_3$) which are very equal to those of case 1 (Fig. 5, left). In this patient, serum albumin levels were maintained by adequate parenteral replacement and bilirubin level was within normal limits. Postoperative course was satisfactory.

In cases 1 and 2, the degrees of liver cirrhosis and the contents of mitochondrial cytochrome a(+a$_3$) were similar to each other. However, a marked hypoalbuminemia and hyperbilirubinemia were noted in case 1 subjected to extended right hepatectomy while such findings were not observed in case 2 with right hepatectomy. Hypoalbuminemia and hyperbilirubinemia appear to be directly related to the massiveness of hepatic resection. A right hepatic resection was well tolerated but a much more extensive resection of the liver was not. When mitochondria from both lobes have cytochrome a(+a$_3$) contents more than 1.4 × 10^{-10} moles per mg protein, net energy producing capacity of liver appears to be strongly dependent upon mitochondrial metabolism of all hepatic

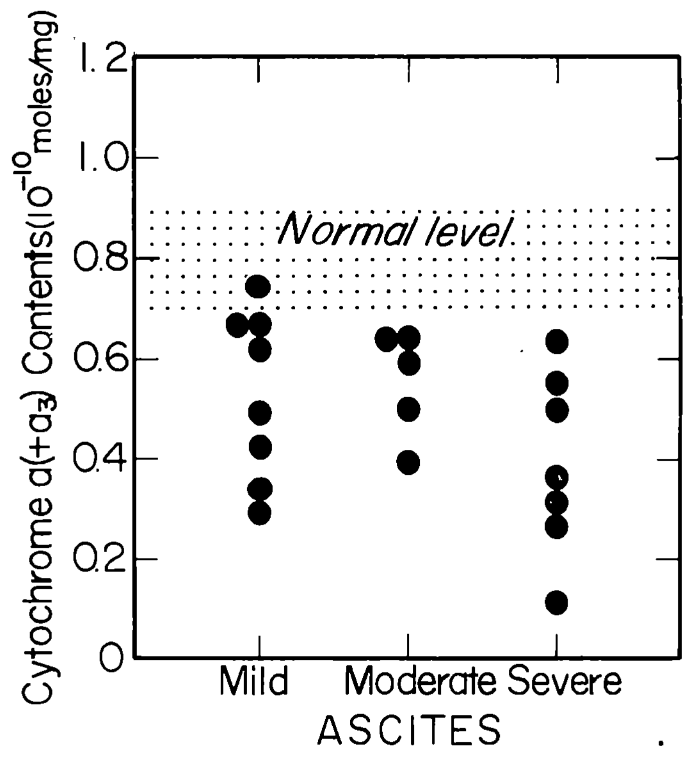


FIG. 4. Relation of cytochrome a(+a$_3$) contents to amounts of ascites. mild, <500 ml of ascites; moderate, >500; severe, >1000.

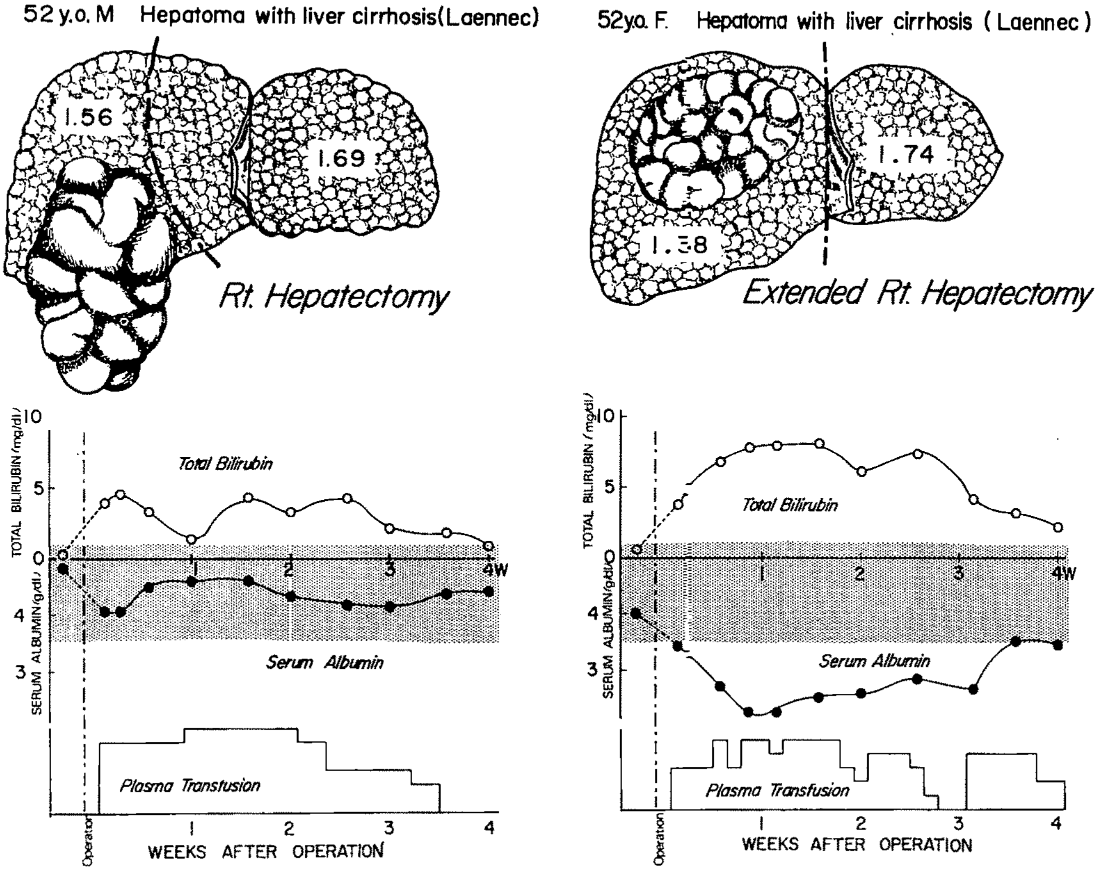


FIG. 5. Postoperative course of the patients with Laennec's cirrhosis subjected to right hepatectomy and extended right hepatectomy. Numbers in figures of the liver show the contents of mitochondrial cytochrome $a(+a_3)$ (10^{-10} moles per mg protein).

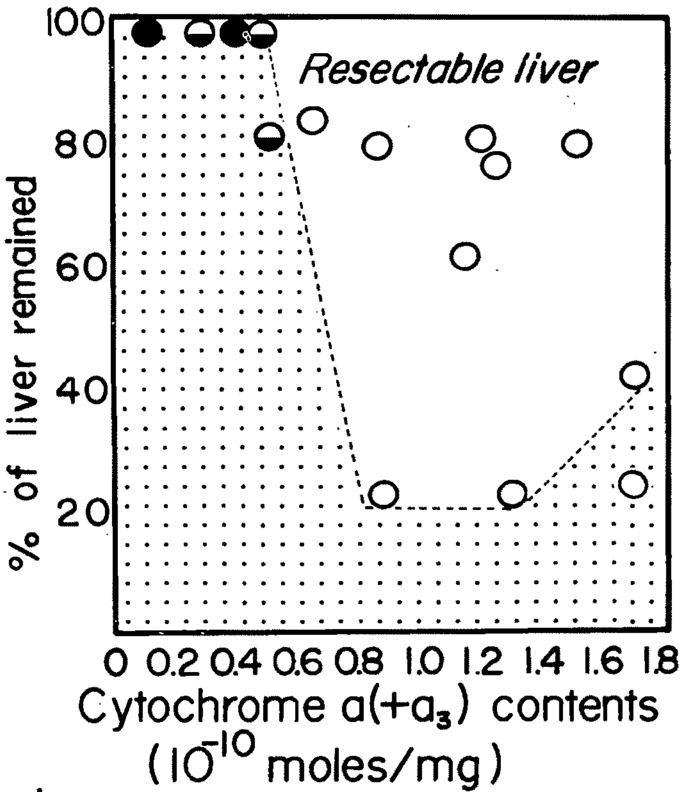


FIG. 6. Schematic representation of relation of cytochrome $a(+a_3)$ contents to the extent of hepatic resection. ○—uneventful postoperative course. ◒—postoperative complication. ●—operative death.

parenchyma containing not only the lobe without cancer but the tumor bearing lobe. The more conservative resections should be performed in such patients.

Figure 6 is a schematic representation of the relationship between per cent of liver resected and the contents of cytochrome $a(+a_3)$ of mitochondria from the remaining liver. As far as the contents of cytochrome $a(+a_3)$ of mitochondria from the remaining liver is from 0.7 to 1.3 × 10^{-10} moles per mg protein, major hepatic resection could be performed without complication and death. Patients with marked increase of cytochrome $a(+a_3)$ content more than 1.5 × 10^{-10} moles per mg protein in both lobes are less ideal operative candidates than those depicted above and the percentage of liver resection should be less than 60%. When the contents of cytochrome $a(+a_3)$ is less than 0.5 × 10^{-10} moles per mg protein, even the supposedly "minor" removal of 15–20% of liver should be avoided.

Discussion

Metabolic derangement following liver resection, although it may be transient, occurs after any sizable resection e.g. hypoglycemia, decrease in serum albumin and prothrombin, increase in serum transaminase and alkaline phosphatase, and hyperbilirubinemia. Those are the result of an increased load upon the reduced number of liver cells. In order that an exact judgement for or against resection can be made at the operation, the metabolic tolerance and regenerative ability of the remnant of liver tissue to adapt itself to functional demands must be appreciated prior to liver resection. However, the preoperative changes of BSP, prothrombin time, SGOT, bilirubin or serum albumin did not correlate well with changes of mitochondrial cytochrome a(+a_3) contents and postoperative complications and mortality. Therefore, no routinely used liver function test seemed to quantitatively assess the functional reserve of the remaining liver nor predict the prognosis. On the other hand, this study suggests that there is a measurable entity that can be described as functional reserve of the remaining liver. Although no sweeping conclusion can be drawn from the results of so small a series of patients, evaluations of the capabilities of the remnant could be made by measurement of cytochrome a(+a_3) content. It is well recognized that a progressive fall in serum albumin level and an increased amount of ascites are poor prognostic signs following hepatic resection. These findings seem consistent with the facts that the postoperatively prolonged hypoalbuminemia and a great amount of ascites were most frequently encountered in the patients with the contents of cytochrome a(+a_3) less than 0.5 × 10^{-10} moles per mg protein. Such patients also showed the shortest survival following laparotomy. Therefore, the results provide us with the view that not only a decrease of cytochrome a(+a_3) contents correlates with a worsening of hepatic functional reserve, but it indicates a poor prognosis.

On the other hand, in general, it has been reported that the cirrhotic liver not only has a reduced tolerance to massive resection, but also, has limited capacity to fully regenerate.[4,16] For these reasons, only the more conservative resections are thought appropriate in such patients. However, in patients with liver cirrhosis, the contents of mitochondrial cytochrome a(+a_3) ranged widely from 0.1 to 1.7 × 10^{-10} moles per mg protein. The cirrhotic patients with cytochrome a(+a_3) contents more than those of normal human liver could tolerate major liver resection in a manner comparable to the non-cirrhotic patients, indicating that certain widespread preconceived attitudes toward the patient with hepatic cirrhosis should be reexamined. Consequently, it is not unreasonable to accept that in the cases in which the contents of cytochrome a(+a_3) of the mitochondria from the liver remnant are within normal limits or more, major hepatic resection can be successfully performed whether associated with liver cirrhosis or not, while patients with marked decrease of cytochrome a(+a_3) could not tolerate even minor operation and have a very high operative mortality.

The precise cause initiating such changes in the contents of cytochrome a(+a_3) is not yet known, but, when regeneration is initiated, energy consuming reactions necessary for the process of regeneration are very active.[1] Whatever the basic trigger, it appears that liver mitochondria could increase energy producing capacity with increasing the contents of respiratory enzymes in order to provide sufficient energy necessary for the increased metabolic demands, as seen in the adaptation of rat skeletal muscle to strenuous running.[5] As far as this study is concerned, the residual liver with the contents of cytochrome a(+a_3) from 0.8 to 1.3 × 10^{-10} moles per mg protein appears to be able to quickly adapt itself by use of enormous energy expenditures to the additional metabolic overload placed upon it from the moment the liver is excised. However, it seems likely that the remaining liver with the contents of cytochrome a(+a_3) more than 1.5 × 10^{-10} moles per mg protein can not be so quickly adapted to an increased metabolic demand. On the other hand, considering that mitochondria with the contents of cytochrome a(+a_3) less than 0.5 × 10^{-10} moles per mg protein had marked reduction in the respiratory control ratio and P:O ratio,[12] the energy production by those mitochondria appear to be remarkably inhibited and not sufficient to induce liver regeneration and to maintain life. As formation of cytochrome a(+a_3) is dependent on mitochondrial protein synthesis,[13] a decrease of cytochrome a(+a_3) contents appears to be due to suppression of the synthesis. However, this criterion cannot be expected to fit for markedly icteric patients with liver cancer, because in mitochondria from the icteric liver the contents of respiratory enzymes often increase remarkably but the electron transfer is inhibited by obstructive jaundice.

More recently, from the observation that amounts of cytochrome a(+a_3) per unit wet weight of liver reflect those in mitochondria, we have developed a quantitative and rapid method, which is technically simpler, for the determination of cytochrome a(+a_3) content in liver homogenate.[17] In our department a careful assay of cytochrome a(+a_3) using about 200 mg of biopsy material have routinely been done prior to contemplated major hepatic resection.

Addendum

Two patients (3 and 4 in Table 1) died of recurrence of tumor, proven by a high and rapid increase in serum α-fetoprotein, 2 and 7 months after operation, respectively.

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Postoperative Hypoxemia in Obese Patients

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Although obese patients represent a high risk group and reports document the occurrence of sudden unexplained deaths in the early postoperative period, no data exist to delineate the existence, extent or duration of hypoxemia in obese subjects. Twenty adults undergoing jejunoileal bypass for morbid exogenous obesity, with a mean weight of 144.0 ± 24.7 kg and a mean age of 34.1 ± 8.3 years, were studied. While breathing room air, arterial blood was collected from each patient, placed in ice and analyzed within ten minutes. A preoperative sample was taken; then samples were analyzed two hours postoperatively and on postoperative days one through five. Preoperatively in the obese patients there was a significant reduction in arterial oxygen tension, mean 75.1 ± 11.1 mm Hg, as against 92.4 ± 4.0 mm Hg in control patients matched for age. There was also a difference in the slope of the regression equation of PaO_2 vs. age; the regression coefficient being significantly greater in the obese group (0.9 vs. 0.46). Postoperatively there was a further fall in PaO_2. Decrease in mean PaO_2 in the obese group in mm Hg averaged −9.2 two hours postoperatively ($p < 0.001$), −15.0 on day one ($p < 0.001$), −15.5 on day two ($p < 0.001$), −11.7 on day three ($p < 0.001$) and −5.1 on day four ($p < 0.01$). $PaCO_2$ was not significantly different from the preoperative control. Base excess was elevated on days two, three and four; 3.1 mEq/L ($p. < .001$), 3.6 mEq/L ($p < .001$) and 1.9 mEq/L ($p < .05$) respectively. Our findings indicate that in obese patients: 1) Preoperatively the fall in PaO_2 with increasing age is greater than in control subjects; 2) Starting with a low basal PaO_2 during postoperative days one through four, the fall in CaO_2 often reaches dangerous levels; and 3) Elevation of blood buffer on days two, three and four can further depress respiration at a time when the PaO_2 has been shown to be at its lowest levels. This hypoventilation due to metabolic alkalosis can further accentuate the already existent hypoxemia. Because of these findings, we suggest careful monitoring of arterial blood gases in obese patients and the administration of oxygen and appropriate electrolyte solutions postoperatively to reduce the increased morbidity and mortality.

For many years there have been reports of arterial desaturation after open chest surgery,[3,7] and postoperative hypoxemia, for a time, was regarded as peculiar to that specialty. However, in 1962 Nunn and Payne[9] demonstrated that hypoxemia may occur in the first few hours after any major operation. This early hypoxemia (the first 6–8 hours following general anesthesia and operation), has been extensively studied and found to be associated primarily with the reversal of the anesthetic causes of hypoxemia, eg. respiratory depression due to anesthetic agents, narcotics, and muscle relaxants; they reflect pharmacologic changes, and are usually of short duration.[10] On the other hand, late hypoxemia (present at 24 hours and often continuing up to seven days or more) is influenced more by the patient's general physical status and the site of operation; it often reflects underlying intrinsic disease processes which are often not so immediately reversible.[1]

Although data are available suggesting postoperative hypoxemia from day one to five in non-obese subjects,[10] there are no data currently available to delineate the existence, extent, or duration of hypoxemia in markedly obese patients. The present study was designed to gather these data.

Method

Sixteen female and four male patients undergoing elective jejunoileal bypass for morbid, exogenous obesity consented to participate in this study. The incision was identical for all subjects: supraumbilical, transverse. All subjects were free of primary cardiorespiratory disease, although 30% were smokers. Their ages ranged 21–49 years, heights 157–190.5 cm, and body weights 104–200 kg.

For each patient preoperative (control) arterial blood gas values were obtained a few days before surgery with the patient unsedated; measurements were obtained both in the supine and in the sitting (upright) position. The arterial samples were obtained after breathing room air for fifteen minutes in each position. All postoperative samples were obtained (after breathing room air for 15 minutes) with the patient 45 degrees upright in bed. The radial artery was cannulated after induction of anesthesia for intra- and postoperative arterial blood gas measurements and for continuous blood pressure monitoring. This cannula was

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usually removed 48–72 hours postoperatively. Arterial blood was collected into iced heparinized plastic syringes and analyzed within five to ten minutes by a single technician in our research laboratory using an Instrumentation Laboratory Model 213 blood gas analyzer. Arterial blood was analyzed for PO_2, PCO_2, and pH, and the raw data corrected when necessary for patient-electrode temperature difference. Base excess was calculated using the Severinghaus slide rule (Radiometer Blood Gas Calculator) employing measured pH, $PaCO_2$, and hemoglobin concentration.

Preoperatively, pulmonary function tests, corrected to body temperature and pressure fully saturated (BTPS) were performed in the seated position using a spirometer. Vital capacity (VC), forced expiratory volume in one second ($FEV_{1.0}$), maximum midexpiratory flow rate (MMEF), and expiratory reserve volume (ERV), were obtained. Girth was measured in the standing position at the level of the umbilicus at normal end (resting) exhalation.

Results

Physical characteristics and the most consistently abnormal pulmonary function test, ERV, are shown in Table 1; the mean arterial blood gas measurements are presented in Table 2. Preoperatively in these subjects with morbid exogenous obesity in the supine position, there was a significant reduction in arterial oxygen tension, mean ± standard deviation, 75.1 ± 11.1.

According to Sorbini,[12] in *supine* non-obese subjects the regression of arterial PO_2 with age is:

$$PaO_2\ (\text{mm Hg}) = 107 - 0.43 \times \text{age (years.)}$$

Standard error of the estimate (S.E.E.) ± 4 mm Hg. The regression of arterial PO_2 with age calculated from our data in *supine* preoperative morbidly obese subjects is:

$$PaO_2\ (\text{mm Hg}) = 105.1 - 0.9 \times \text{age (yrs.)}$$

$$\text{S.E.E. (8.6 mm Hg)}$$

The rate of decline of PaO_2 with advancing age (regression coefficient) is statistically dissimilar in the two equations, although there is no difference in the calculated constant between equations. Figure 1 presents the PaO_2 versus age correlation graphically for non-obese and obese subjects.

The regression of arterial PO_2 with age calculated from our data in *seated*, preoperative morbidly obese subjects is:

$$PaO_2\ (\text{mm Hg}) = 84.4 - 0.3 \times \text{age (yrs.)}$$

$$\text{S.E.E.} = 4.1 \text{ mm Hg}$$

$$(r = -0.6,\ p < .01)$$

This equation is not dissimilar from data previously reported by one of the authors.[16]

Data for blood gas measurements at pre- and selected postoperative times are shown in Table 2. Figure 2 presents this data graphically with 95% confidence bands. Starting at a reduced preoperative arterial oxygen value, there was a further fall in PaO_2. Decrease in mean PaO_2 in these obese subjects measured in mm Hg averaged −10.4 two hours postoperatively ($p < 0.001$), −16.6 on postop day one ($p < 0.001$), −17.2 on day two ($p < 0.001$), −13.3 on day three ($p < 0.001$), −6.7 on day four ($p < 0.01$), and −2.5 on day five ($p < .05$) (Table 3). Comparable reductions in postoperative PaO_2 are seen in Table 4, where preoperative control

TABLE 1. *Physical Characteristics*

Patient No.	Sex	Age	Actual Weight (kg)	Ideal Wt. (kg)*	% of Ideal Wt.	Girth (cm)	Ht. (cm)	G/H ratio	Wt (kg) / Ht (cm)	ERV (L)	% Pred. ERV†
1	M	48	164	80.0	205.0	147.3	190.5	0.773	.861	—	—
2	M	23	200	63.9	313.0	172.7	170.2	1.01	1.18	0.649	32.6
3	F	39	125	54.3	230.2	144.8	162.6	0.89	.769	0.468	42.7
4	F	38	127	55.9	227.2	144.8	165.1	0.877	.769	0.560	50.3
5	F	43	125	63.5	196.9	124.5	175.3	0.710	.713	0.540	39.0
6	F	26	128	58.0	220.7	118.1	168.9	0.699	.758	0.758	52.0
7	F	29	104	52.7	197.3	134.6	160.0	0.841	.650	0.517	41.0
8	M	49	148	63.5	233.1	152.4	175.3	0.869	.844	0.528	33.6
9	F	31	160	52.7	303.6	157.5	161.3	0.976	.992	0.445	38.2
10	F	39	154	54.3	283.6	167.6	162.6	1.03	.947	0.379	34.5
11	F	29	168	52.7	318.8	160.0	160.0	1.00	1.05	0.446	37.8
12	F	26	126	61.6	204.5	138.4	172.7	0.801	.730	1.180	94.9
13	F	35	166	55.9	297.0	162.6	165.1	0.985	1.01	0.336	29.5
14	F	21	116	55.9	207.5	137.2	166.4	0.825	.697	0.831	65.4
15	F	33	148	54.3	272.6	156.2	162.6	0.961	.910	0.687	59.7
16	F	49	128	58.0	220.7	141.6	167.4	0.846	.765	0.267	26.1
17	F	31	136	58.0	234.5	127.0	167.1	0.760	.814	0.513	43.0
18	F	28	182	55.9	325.6	160.0	164.6	0.972	1.11	0.379	31.3
19	M	32	157	69.5	225.9	150.0	178.0	0.843	.882	1.492	77.6
20	F	34	117	51.4	227.6	127.0	157.0	0.809	.745	0.821	72.9
Mean		34.1	144.0	58.6	247.3	146.2	167.6	0.874	0.859	.621	45.1
S.D.		8.3	24.7	6.9	44.0	15.2	7.8	0.102	0.146	.301	21.0

° From table of desirable weights (medium frame), Metropolitan Life Ins. Co., 1959.

† Predicted from age and height.[2]

TABLE 2. *Arterial Blood Gas Measurements (Room Air) at Various Times (N = 20)*

Time		Variable (mean ± standard deviation)		
		PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	Base Excess (mEq/L)
Preoperative (control)	upright	73.5 ± 5.3	37.2 ± 2.6	1.4 ± 2.4
	supine	75.1 ± 11.1	35.3 ± 3.3	0.7 ± 2.6
PAR*		64.3 ± 6.9	35.4 ± 2.7	−2.5 ± 2.4
Postoperative				
Day 1		58.5 ± 8.8	37.6 ± 4.4	2.0 ± 2.5
Day 2		58.0 ± 9.3	38.4 ± 4.0	4.5 ± 4.0
Day 3		61.8 ± 9.0	39.0 ± 3.8	4.9 ± 2.3
Day 4		68.4 ± 8.0	35.6 ± 3.3	3.3 ± 3.3
Day 5		72.6 ± 7.1	38.1 ± 3.9	2.4 ± 3.0

* Postanesthetic Recovery Area (2–4 hours postop).

arterial blood gases were measured in the upright position.

A step-wise linear regression of the minimum postoperative PaO_2 value on the six criteria: 1) preop (supine) PaO_2; 2) age; 3) weight; 4) weight/height (wt/ht) ratio; 5) girth/height (G/H ratio); and 6) predicted ERV, revealed that the best prediction is obtained from either the G/Ht or Wt/Ht ratio, and that the other criteria do not significantly improve the prediction. The equations based on our data are:

$$\underset{\text{(mm Hg)}}{\text{minimum } PaO_2} = 31.9 + 27.7 \times (\text{G/Ht}) \qquad \text{S.E.E.} = 7.3$$

or

$$\underset{\text{(mm Hg)}}{\text{minimum } PaO_2} = 39.5 + 19.3 \times [\text{Wt (kg)/Ht (cm)}] \qquad \text{S.E.E.} = 7.3$$

These equations were significant at $p < .05$.

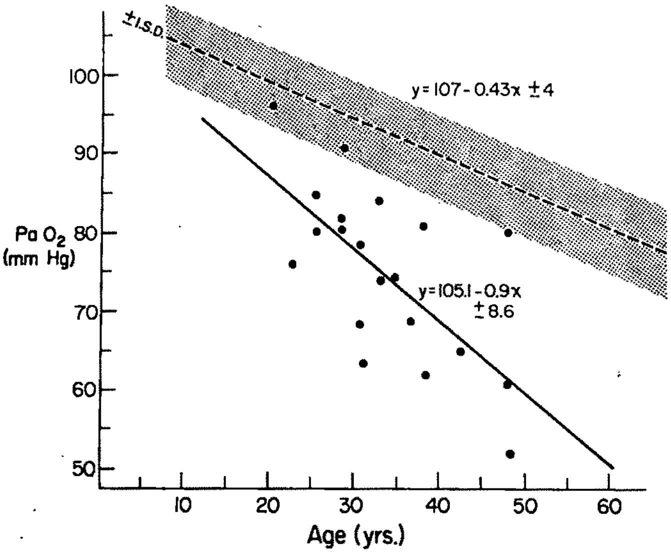

FIG. 1. Effect of age (yrs.) on the PaO_2 (awake, supine, breathing room air) in normal versus morbidly obese patients. Interrupted line (normal, nonobese) from Sorbini.[12] Solid line is from present study in morbidly obese patients (n = 20).

$PaCO_2$ was significantly increased above the preoperative control on postoperative days two [3.2 mm Hg ($p < .05$)], three [3.7 mm Hg ($p < .01$)], and five [2.8 mm Hg ($p < .05$)]. There was a significant reduction in base excess measured two to four hours postoperatively in the recovery room area, −3.1 mEq/L ($p < 0.01$). Base excess in mEq/L was elevated on postoperative days two, three, and four: +3.7 ($p < 0.001$), +4.2 ($p < 0.001$), +2.5 ($p < 0.05$) respectively (Table 3).

Preoperative measurement of forced vital capacity, forced expiratory volume in one second, and maximum midexpiratory flow rate did not demonstrate significant restrictive or obstructive pulmonary dysfunction in any of our obese subjects. Therefore, these data are not included here.

Discussion

Although in non-obese individuals postoperative hypoxemia is a well-recognized complication of intrathoracic and intraabdominal surgery, its importance in the markedly obese patient is less well recognized.

The finding of preoperative hypoxemia in our subjects is consistent with previous reports.[11] Uneven ventilation is

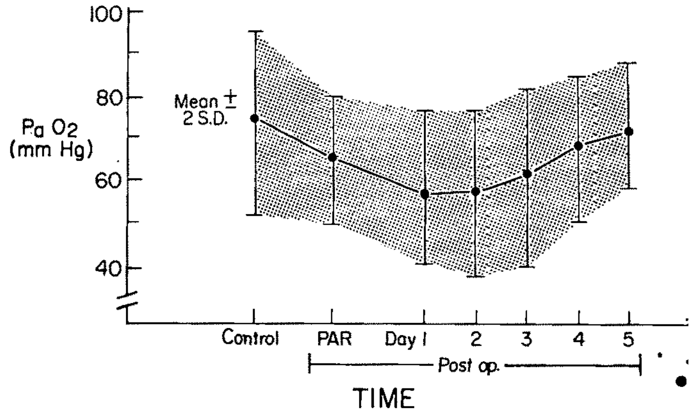

FIG. 2. Graphic representation of the fall in PaO_2 (mm Hg) with time postoperatively. Solid line is mean; stippled area is ± 2 standard deviations.

TABLE 3. *Mean Differences of Blood Gas Measurements at Selected Times Postop (45 Degrees Upright) from Preop (Supine) Values (N = 20)*

	Variable		
Time	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	Base excess (mEq/L)
PAR°	−10.4†	0.1‖	−3.1‡
Postoperative			
Day 1	−16.6†	2.4‖	+1.3‖
Day 2	−17.2†	3.2§	+3.7†
Day 3	−13.3†	3.7‡	+4.2†
Day 4	−6.7‡	0.4‖	+2.5§
Day 5	−2.5‖	2.8§	+1.7‖

° Postanesthetic Recovery Room (2–4 hours postop).
† Significant at $p < .001$.
‡ Significant at $p < .01$.
§ Significant at $p < .05$.
‖ Not significant at $p > .05$.

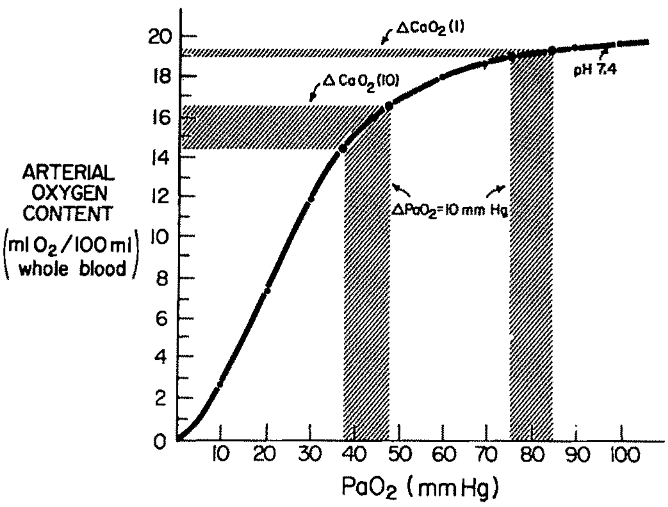

FIG. 3. Hemoglobin-oxygen dissociation curve (pH = 7.4, $PaCO_2$ = 40 mm Hg). A 10 mm Hg fall in PaO_2 (85 to 75 mm Hg) on the upper part of the curve reflects a change in arterial oxygen content (CaO_2) of one unit as compared to an equal fall in PaO_2 (10 mm Hg) from 48 to 38 mm Hg on the more vertical portion of the same curve would yield a 10 unit reduction in arterial oxygen content.

recognized as the most important contribution to this hypoxemia.[5] The shallow breathing of the markedly obese at a small lung volume (reduction of functional residual capacity [FRC] at the expense of ERV) causes small airway closure with regional overperfusion in relationship to ventilation leading to increased venous admixture. In conscious subjects in the supine position, the degree of airway closure and gas trapping is greater in obese subjects,[4] presumably because this added weight to the thoracic cage reduces lung volume. Age,[12] weight (via abdominal obesity),[11] smoking habits,[14] and position,[6] all influence gas exchange by way of their effects on small airway closure.

However, the marked influence of advancing age, plus obesity, on the rate of decline of the *supine* PaO_2 (regression coefficient of −0.9) suggests that the older morbidly obese patient would be in a very high risk category when predicting the level of postoperative PaO_2. When arterial oxygen tension is reduced, normal compensatory mechanisms operate increasing cardiac output to facilitate tissue oxygen delivery. This required increase in cardiac output may be severely limited in an older patient with obesity related diseases (hypertensive cardiovascular disease, coronary artery disease, and advanced atherosclerosis secondary to diabetes mellitus). Our findings of a progressive fall in PaO_2 postoperatively further corroborate the increased demand placed on this cardiovascular compensatory mechanism.

TABLE 4. *Mean Differences of Blood Gas Measurements at Selected Times Postop (45 Degrees Upright) from Preop (Upright) Values (N = 20)*

	Variable		
Time	PaO_2	$PaCO_2$	Base
PAR°	9.2†	−1.8§	−3.9†
Postoperative			
Day 1	15.0†	0.5‖	0.7‖
Day 2	15.5†	1.3‖	3.1†
Day 3	11.7†	1.8‖	3.6†
Day 4	5.1‡	−1.5‖	1.9§
Day 5	0.9‖	1.0‖	1.1‖

° Postanesthetic recovery room (2–4 hours postop).
† Significant at $p < .001$.
‡ Significant at $p < .01$.
§ Significant at $p < .05$.
‖ Not significant at $p > .05$.

This study confirms previous reports of arterial hypoxemia persisting up to five days after upper abdominal surgery.[10] Alexander[1] has shown that the changes in arterial PO_2 parallel a fall in FRC following various types of surgery. The extent of this reduction depends on the site of operation, being most severe after upper abdominal surgery and least severe following surgery on the extremities. Our data showing the occurrence of minimal PaO_2 values on postoperative days one and two (Fig. 2) are consistent with previous studies in non-obese patients.[10] However, of particular concern is the portion of the hemoglobin-oxygen dissociation curve at which these obese individuals function post-operatively. Figure 3 presents the effect of a 10 mm Hg reduction in PaO_2 on the horizontal versus the vertical portion of the hemoglobin-oxygen dissociation curve. Since these obese patients function postoperatively on the more vertical position of this curve, small reductions in arterial oxygen tension are reflected in a marked fall in arterial oxygen content (CaO_2) (Figure 3). If to this reduction in CaO_2 any increased metabolic need for O_2 (increased body temperature) is added, the potential for respiratory failure increases.

Considering acid-base balance, it is well recognized that a mixed respiratory and metabolic acidosis may occur early following surgery. Early workers[13] attributed the

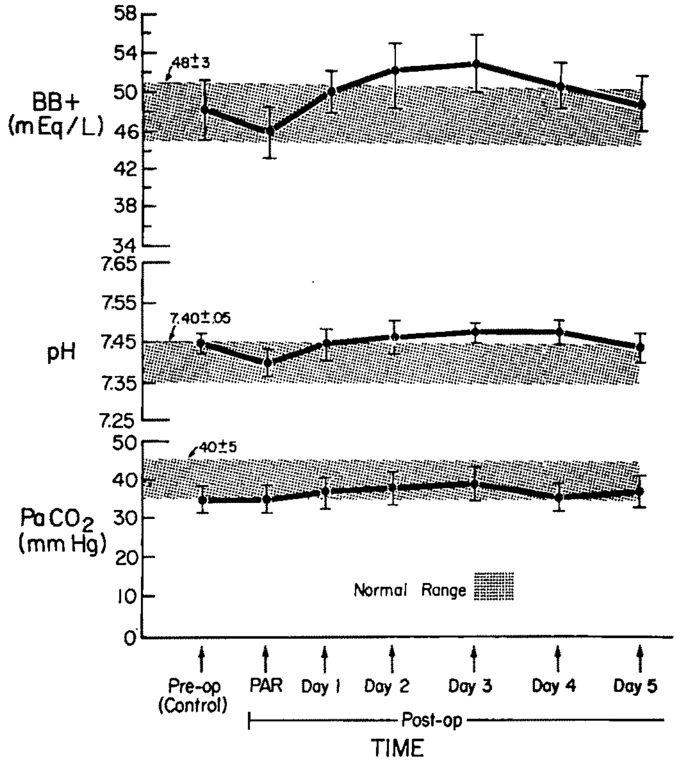

FIG. 4. Representation of the change in acid-base status with time postoperatively. Solid lines are mean with ± 2 standard deviations. Note the elevated blood buffer base (BB) on post-op days two, three and four with the simultaneous rise in pH without a significant rise in Pa CO_2. These findings confirm the development of a postoperative metabolic alkalosis.

postoperative acidosis to hypoventilation secondary to the respiratory depressant effect of the anesthetic agents used. Other workers[15] supported this view and pointed out that the acidosis following thoracic surgery was more pronounced than that seen after abdominal surgery. We found a mean reduction in buffer base of −2.4 mEq/L (Table 2) while the simultaneous mean $PaCO_2$ was 35.4 mm Hg. These measurements were made two to four hours after arrival in the post-anesthetic recovery room (PAR). This induced metabolic acidosis could be the result of sympathoadrenal activation. Interference with oxidative processes with consequent accumulation of intermediary metabolites may also occur.[8] Other factors that could contribute to metabolic acidosis include poor tissue perfusion due either to hypotension, hypovolemia, or vascular occlusion with impaired renal function. In our patients there was no reason to implicate poor circulatory status since both intra-arterial pressure was normal, blood loss was consistently less than 10% of estimated blood volume, and fluid administration was carefully monitored. In addition, urine acetone determinations were normal and urine output was always greater than 50 ml per hour in the postoperative recovery room. One cannot speculate usefully on the exact cause of the metabolic acidosis in the present study, but it was definitely shown to spontaneously correct itself without specific therapy during the first 18–24 hours postoperatively.

Blood buffer base was shown to be statistically elevated on postoperative days two, three and four with return to within normal limits by the fifth postoperative day (Fig. 4). The most plausible explanation for these changes was the loss of hydrogen ion (H+) through continuous nasogastric suction, a well-recognized cause of metabolic alkalosis. Since lactated Ringer's solution was utilized intraoperatively, its metabolized lactate could contribute initially to the alkalosis, but in the postoperative period intravenous fluids were limited to saline and dextrose in water. Lending further credence to this explanation is the fact that the nasogastric tube was removed almost always on the morning of the fourth postoperative day. Subsequently, on postoperative day five, the mean elevation of buffer base was not statistically different from control preoperative values (Fig. 4).

The significant clinical implication of our postoperative arterial blood gas findings in relation to one another can be thought of as follows:

1) Starting with a low basal PaO_2, during postoperative days one through four, the fall in CaO_2 often reaches dangerous levels;

2) Elevation of blood buffer base on days two, three and four can further depress respiratory drive at a time when the PaO_2 has been shown to be at its lowest levels; and

3) This hypoventilation due to metabolic alkalosis can further accentuate the already existent hypoxemia.

In view of these findings, it would appear prudent to carefully monitor arterial blood gases in markedly obese patients in order to guide postoperatively the administration of oxygen and appropriate electrolyte containing solutions. This increased vigilence could possibly reduce the already reported increased morbidity and mortality postoperatively in these morbidly obese patients.[17]

Acknowledgments

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Thrombophlebitis and Thromboembolism:

Results of a Prospective Study

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Thrombophlebitis leading to pulmonary embolism has been stated to cause as many as 9% of hospital deaths. Its diagnosis, sites of common occurrence, treatment and immediate sequelae have long been controversial subjects. A prospective study of thrombophlebitis was set up to evaluate these problems. One hundred and sixty-six patients diagnosed clinically as having thrombophlebitis or pulmonary embolus were studied with the ultrasonic flow detector (doppler). To assess the stated accuracy of this instrument, venograms were done when possible. The doppler proved in this series to be 93% accurate as compared to venography which is comparable to other series. Pulmonary scans and angiograms were obtained from patients suspected of having pulmonary emboli. Results were as follows: 1) Of 113 patients suspected of having thrombophlebitis clinically, only 26 (23%) of the cases were confirmed by doppler; 2) Of 53 patients suspected of having pulmonary embolus clinically, only 18 (34%) had confirmation by scan, angiogram or doppler; 3) Of 39 patients in this series who had thrombophlebitis, 11 (23%) were not suspected of having lower extremity venous disease until pulmonary embolus occurred, 4) Calf vein thrombosis without additional proximal occlusion was present in only 10% of cases; and 5) Thirty per cent of doppler or venographically proven cases of thrombophlebitis occurred after orthopedic injuries or operations. It was concluded that physical examination alone was grossly inaccurate in determining the recurrence of lower extremity thrombosis. In fact physical examination alone appeared to select out for treatment large numbers of patients without venous disease while a significant number of patients with thrombophlebitis remained clinically asymptomatic until pulmonary embolism occurred. Most deep venous disease was found in the larger veins above the knee, explaining the paucity of diagnostic symptoms in these individuals. The ultrasonic flow detector was found to be an extremely accurate, simple and rapid bedside test that could be applied daily to the high risk groups. The appearance of thrombosis could then be treated with heparin with excellent prospects of preventing occurrence of pulmonary embolus.

THROMBOEMBOLIC DISEASE has been shown to be one of the leading causes of hospital death. Orlow has estimated that 5% of all hospitalized patients suffer from venous thrombosis.[11] In one series, 9% of autopsied postoperative deaths were due to pulmonary embolus.[1] In addition, the long term sequela of thrombophlebitis, venous insufficiency, is a common and extremely debilitating disease. The recent emphasis on relatively noninvasive diagnostic instruments has lead to a variety of bedside techniques to evaluate venous thrombosis.

Examination with one of these, the ultrasonic flow detector (doppler), has been shown to be extremely accurate in the detection of venous occlusion.[12-14] This instrument was used in conjunction with venography, pulmonary angiography, and pulmonary scanning to study thromboembolic disease prospectively. Efforts were made to evaluate the following problems: 1) The accuracy of history and physical examination in predicting the presence of thromboembolic disease; 2) The individual accuracy of commonly used signs and symptoms in predicting the presence of venous thrombosis clinically; 3) Frequency of involvement of various lower extremity venous segments in thrombophlebitis; 4) Identification of high risk groups in regards to venous thrombosis within the hospital population; and 5) Efficacy of heparin in the prevention of pulmonary embolis and recurrent thrombophlebitis.

Methods

Patients included in this study were: 1) All those admitted to the hospital suspected clinically as having venous thrombosis; and 2) All those who developed signs and

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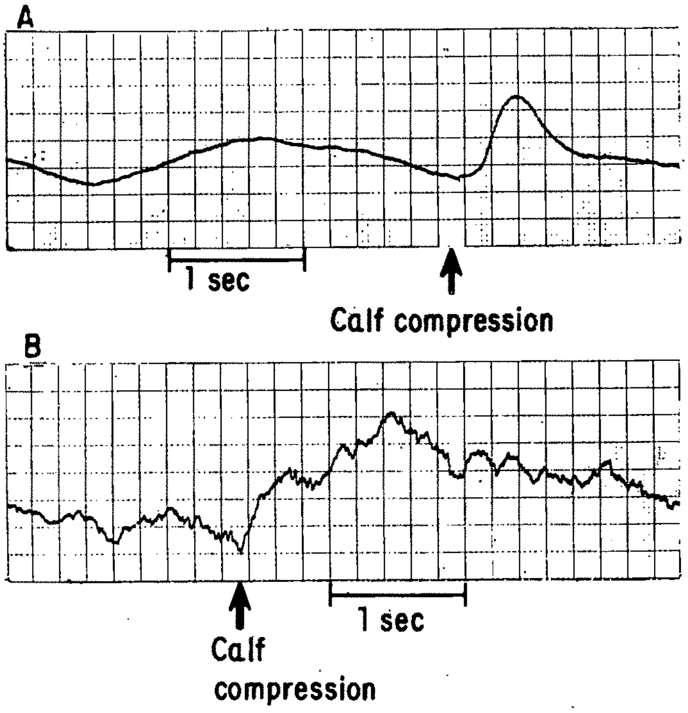

FIG. 1. Effects of distal compression of the lower extremity on common femoral vein flow.

symptoms or were suspected of having pulmonary embolus. All patients admitted to the study were evaluated clinically by a housestaff physician and a trained technician. A doppler examination was performed on every patient. Documented thrombophlebitis was treated with 10–14 days of heparin or on rare occasions by Coumadin. The method of ultrasound examination used combines the methods described by Sumner and Siegel,[12-14] and is summarized as follows: Each site, posterior tibial, popliteal, superficial femoral, and common femoral at the groin crease is examined bilaterally. Symmetry between the two lower extremities is present unless cellulitis, edema, or other local factors are present. The examiner looks first for phasic flow with respiration at each of the four sites bilaterally, expecting decreased flow velocity with inspiration, increased with expiration. The presence of continuous flow, or rarely, no flow indicates obstruction. An immediate increase in flow velocity with compression at a point distal to the vein monitored by the probe is expected in normal veins as contrasted to a slow attenuated rise in the presence of venous obstruction (Fig. 1). Digital compression over the main deep vein proximal to the part monitored by the probe will produce immediate cessation of flow in normal veins and no effect or a slow decrease in velocity if venous flow is directed through collaterals. The greater saphenous vein acts as a major collateral in deep venous occlusion in the area of the knee. Marked increase in saphenous vein velocity in this area is suggestive of superficial femoral or popliteal thrombosis. Marked increase in flow velocity in the saphenous collaterals across the groin usually verifies iliofemoral occlusion in conjunction with an altered (continuous) or absent common femoral signal. The inferior epigastric vein, which runs across the groin in a position overlying the femoral vein may often be confused with the femoral vein by the inexperienced examiner. Occasional reverse flow in the posterior tibial veins indicates proximal occlusion. The main diagnostic criterion are summarized in Fig. 2.

To confirm the high degree of accuracy attributed to the doppler, venograms were obtained when possible. Fifty-five venograms were performed. The doppler diagnosis was confirmed in 51 of these cases (93%). Two patients had a

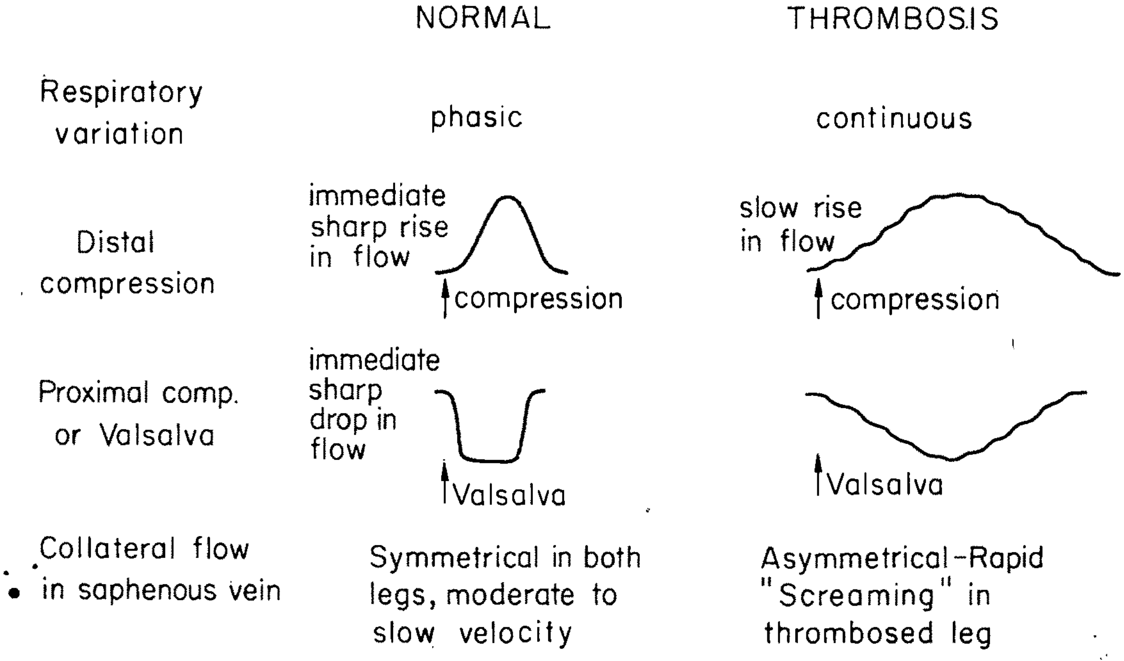
NORMAL
THROMBOSIS
Respiratory variation
phasic
continuous
Distal compression
immediate sharp rise in flow
compression
slow rise in flow
compression
Proximal comp. or Valsalva
immediate sharp drop in flow
Valsalva
Valsalva
Collateral flow in saphenous vein
Symmetrical in both legs, moderate to slow velocity
Asymmetrical-Rapid "Screaming" in thrombosed leg

FIG. 2. Summary of doppler findings in normal lower extremities and those with venous thrombosis.

TABLE 1. *Comparison of Doppler and Venography in Fifty-five Patients Suspected of Having Thrombophlebitis*

	# Cases	Per cent
Agreement of Doppler and Venography	51	93%
Positive Doppler Normal Venogram	3	5%
Negative Doppler Exam, Thrombi Visualized on venography	1	2%

diagnosis of thrombophlebitis made by doppler but the venograms were normal. One patient who was felt to have normal venous dynamics by doppler examination was found to have isolated anterior tibial vein thrombophlebitis by venography. This vein was not routinely examined with the doppler during this study (Table 1).

Results

One hundred and sixty-six patients were studied in a one-year period. The distribution of diagnostic examinations is shown in Table 2. The patients were distributed between two basic groups: 1) Those examined because of clinical suspicion of thrombophlebitis; and 2) Those suspected of having pulmonary embolus in whom a source of embolus was sought (Table 3). One hundred and thirteen patients comprised the group evaluated for thrombophlebitis. When evaluated by venogram or doppler, only 26 patients were found to have objective evidence of disease. The accuracy of clinical diagnosis by the traditional signs (swelling, erythema, pain, and Homans' sign) was therefore only 23% (Table 4).

Fifty-three patients made up the group evaluated for pulmonary embolus. Of these cases 35 were proved not to have this disease by the presence of another diagnosis (17), negative scan (13), or negative doppler examination and pulmonary angiogram (5). The accuracy of clinical signs alone was 34% (Table 5).

The remaining 18 patients were judged to have a pulmonary embolus on the basis of a strong clinical history in addition to one or more objective tests. Positive scans or angiograms, or as in two cases positive doppler and clinical signs of shock, in addition to the history was arbitrarily accepted as evidence of pulmonary embolus. Seven patients had a positive scan but the lower extremity venous dynamics were normal. The remaining 11 patients (61%) had a source for the presumed embolus documented by doppler examination or venography (Table 6).

TABLE 2. *Diagnostic Studies Done on 166 Patients Suspected of Having Thrombophlebitis*

Examination	Number	Per cent
Doppler Exam	166	100%
Venograms	55	33%
Pulmonary Scans	29	18%
Pulmonary Angiograms	7	4%

TABLE 3. *Reason for Initial Evaluation*

	Number of Pts.	Per cent
Thrombophlebitis	113	68%
Pulmonary Embolus	53	32%

Of the entire series of 39 patients who had venous thrombosis, it is notable that the 11 patients with pulmonary embolus were not symptomatic enough from their lower extremity disease to arouse suspicion until embolism occurred (28%). Six patients retrospectively had minimal signs which might have suggested venous thrombosis while five patients had no symptoms at all.

The most frequently encountered signs and symptoms in those patients clinically diagnosed as having thrombophlebitis were swelling, erythema, and calf muscle tenderness. Of these signs, only erythema occurred in a significantly greater number of patients who were diagnosed as having thrombophlebitis by venography or doppler examination than normal patients. Swelling occurred in 23% greater frequency in those with thrombophlebitis as in those with normal veins. Tenderness occurred with equal frequency in patients having no venous disease and those who had objective evidence of venous thrombosis. The most worthwhile clinical finding appeared to be the presence of distended superficial collateral veins in the affected leg. These collaterals were noted in 39% of those who had proven thrombophlebitis, and in only 3% of patients who had no venous disease as documented by venography and doppler examination (Table 7).

TABLE 4. *Accuracy of Clinical Diagnosis in Thrombophlebitis and Pulmonary Embolus*

	Number Cases Diagnosed	Cases Confirmed by Objective Tests	Per cent Accuracy
Thrombophlebitis	113	26	23%
Pulmonary Embolus	53	18	34%

TABLE 5. *Patients Evaluated for Pulmonary Embolus in Whom No Embolus was Found*

	Number of Patients	Per cent of Total Number Evaluated for Embolus
Other explanation for clinical findings suggestive of embolus, negative doppler	17	32%
Negative pulmonary scan, negative doppler	11	21%
Negative pulmonary scan, positive doppler	2	4%
Negative pulmonary angiogram, negative doppler	5	9%
Total	35	66%

TABLE 6. *Patients Evaluated for Pulmonary Embolus with Objective Evidence for This Diagnosis*

	Number of Patients	Per cent of Total Number Evaluated for Embolus
Positive pulmonary scan, angiogram, thrombophlebitis by doppler	2	4%
Positive doppler, unequivocal history for embolus, profound shock	2	4%
Positive scan, thrombophlebitis by doppler	7	13%
Positive scan, negative doppler	7	13%
Total	18	34%

TABLE 7. *Accuracy of Signs and Symptoms in Patients Studied: Comparison of Patients with Objective Evidence of Thrombophlebitis and Those Found to Have Normal Veins*

	Thrombi Present		Thrombi Absent	
	Number	Per cent	Number	Per cent
Swelling (thigh) (calf)	27/39	69%	58/127	46%
Erythema	16/39	41%	13/127	10%
Tenderness	12/39	31%	42/127	33%
Prominent superficial collaterals	15/39	39%	4/127	3%

TABLE 8. *Anatomical Site of Thrombus in Patients with Proven Thrombophlebitis*

Site	Number	Per cent
Iliofemoral segment Superficial femoral Popliteal Calf veins	22	56%
Superficial femoral only	1	2.6%
Iliofemoral segment Superficial femoral Popliteal	1	2.6%
Superficial femoral Popliteal Calf veins	3	7.8%
Popliteal Calf veins	7	18%
Popliteal only	1	2.6%
Calf veins only	3	7.8%
Anterior tibial veins only	1	2.6%

TABLE 9. *Early Results of Anticoagulant Therapy in Forty-four Patients Treated for Thrombophlebitis*

	Number	Per cent
Complications		
Mild gastrointestinal bleeding	8	18%
Death	0	0%
Recurrence (in hospital)	1	2%

When diagnosed, most patients with thrombophlebitis had involvement of the veins above the knee (69%). Twenty-two of the 40 cases had involvement of all major deep veins including the iliofemoral segment (56%). Only four patients (10.4%) had isolated calf thrombosis (Table 8).

In most patients in this series no obvious predisposing factors could be isolated. One notable exception, however, were 12 patients (30%) who had lower extremity fractures, trauma, or operations.

During the study, 44 patients received heparin or Coumadin therapy for thrombophlebitis or suspicion of venous thrombosis until confirmatory studies could be done. Heparin was administered by intravenous bolus attempting to maintain the clotting time at twice normal values at one hour preceding the next dose. Coumadin was used mainly on orthopedic patients who had lower extremity operations. Mild gastrointestinal bleeding was the sole complication encountered, occurring in eight patients (18%). No deaths attributable to anticoagulants were noted. Recurrent thrombophlebitis with pulmonary embolus was recorded in one patient several days after heparin was discontinued but the patient did well after a second course of this drug. One patient died of thromboembolic disease during the period of study, the death occurring shortly after admission and before therapy was begun (Table 9).

Discussion

The fact that clinical signs and symptoms alone are inadequate in the accurate diagnosis of thromboembolic disease has been well documented. Haeger reported that only 46% of clinically diagosed cases of thrombophlebitis were confirmed by venography.[7] Evans noted that only 10 of 19 cases of clinically suspected phlebitis (53%) were confirmed by phlebography.[5] Hume *et al.* stated that clinical impressions corresponded with more objective modalities in 54% of cases.[8] Overdiagnosis in clinically suspected disease, however, is overshadowed by the magnitude of symptom free venous thrombosis. One clinical pathological study revealed that 66% of deep thromboses are symptom free.[11] In his study of thromboembolism, Belt stated that 90% of fatal pulmonary emboli in a series of 56 patients had no clinical manifestations of phlebitis.[3] In our present series, the disease was overdiagnosed by a four to one margin by housestaff clinicians. In spite of the wide latitude taken for overdiagnosis in an effort to prevent the mortality from thromboembolism, 11 individuals (28%) with documented thrombophlebitis remained undiagnosed until embolism occurred. The primary reason for difficulty in making the diagnosis of venous thrombosis is that usual clinical signs of the disease; swelling, pain and erythema, occur commonly in individuals with normal veins. Only the presence of distended superficial venous collaterals was a reliable diagnostic finding.

The high incidence of large vein thrombosis found in this study is not surprising in the light of data published by

Mavor. Ninety-three per cent of his cases had involvement of the iliofemoral segment.[9,10] Since Gunnar Bauer popularized the belief that thrombi initially involve the calf veins and propagate proximally, diagnostic efforts have been directed toward the calf veins in hopes of localizing the disease in this area.[2] Mavor's belief that the iliofemoral segment might be involved first and that distal stasis results in further thrombosis, would suggest that diagnostic emphasis be based on the larger veins of the legs.

It is obvious from this study that clinical examination to the lower extremity in a majority of cases is inadequate for the diagnosis of venous thrombosis. In addition, the typical clinical examination may actively select out persons with no venous disease while excluding from consideration those commonly asymptomatic patients with large vein thrombosis. Not only will a large number of patients be needlessly exposed to the small but significant complications of heparin therapy, but these individuals will also carry the stigmata of venous disease throughout their lives. Those with venous thrombosis will very likely remain undiagnosed unless embolism or local complications of venous insufficiency develop.

Diagnostic aids are needed to replace clinical examination. The high degree of accuracy of the ultrasonic flow detector in the diagnosis of thrombophlebitis confirms its usefulness as a simple, immediate bedside technique to evaluate venous patency. Such accuracy and clinical usefulness has been noted by other investigators. Strandness and Sumner reported an overall accuracy of 93% in 67 venographically confirmed cases.[13] Evans (1970) reported a 95% correlation with venography[5] and Siegel noted an overall 86% accuracy again using the venogram as reference standard.[12]

Not only is the device accurate but it allows a simple rapid evaluation that can be performed daily during high risk intervals, as during the early postoperative period. Used in such a manner, thrombophlebitis can usually be diagnosed before embolism occurs. In addition if the clinical history for embolism exists, the doppler is often able to confirm at the bedside the presence of thrombophlebitis, thereby greatly increasing the accuracy of clinical diagnosis of pulmonary embolus. This advantage is self evident in the critically ill patient who might not tolerate even a short stay at the Radioisotope or Catheterization Laboratory.

The controversy surrounding anticoagulant therapy for thromboembolic disease could only be resolved conclusively by a large double-blind study. In this series only one recurrence after anticoagulant therapy was recorded. Although the numbers are not statistically significant, this 2% rate of re-thrombosis agrees with the retrospective study done by Coon *et al.*[4] The complications recorded during the time of this study were those of mild gastrointestinal bleeding. The 18% complication rate is not inconsequential, however. Reports of a high complication rate from the use of anticoagulants, particularly in elderly women, emphasize the importance of accurate diagnosis.[15] The argument that anticoagulants should be used whenever thrombosis is suspected because complications of such therapy are so low may not be entirely accurate.

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Axillary-Axillary Artery Bypass for the Correction of Subclavian Artery Occlusive Disease

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Numerous procedures have been proposed for the correction of symptomatic subclavian artery occlusive disease, none of which have been uniformly accepted by vascular surgeons. During the past 21 months we have successfully treated six patients with symptomatic subclavian artery occlusive disease by the construction of an axillary-axillary artery bypass. There were three complications in this small series, a wound hematoma, a case of median nerve parasthesias, and a late graft thrombosis, possibly caused by external pressure on the graft. These complications have not caused any serious morbidity. All patients have been followed to the present time, all have experienced symptomatic improvement and none has developed any symptoms of donor arm ischemia. Axillary-axillary artery bypass is currently our procedure of choice for the correction of symptomatic subclavian artery occlusive disease because of its effectiveness, absence of serious morbidity and ease of performance.

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SYMPTOMATIC occlusive disease of the subclavian artery has been treated successfully by carotid-subclavian bypass, endarterectomy, aorto-subclavian bypass, subclavian-subclavian bypass, and femoral-axillary bypass. In the past two years several authors have described the use of axillary-axillary artery bypass for subclavian revascularization,[7,8,10-12] but the total reported cases to date include only six patients. We have performed axillary-axillary artery bypass on six patients at this institution in the past 21 months as treatment for symptomatic subclavian artery occlusive disease and feel this procedure offers distinct advantages over alternative methods of subclavian revascularization. The clinical course of these six patients, a description of the operative procedure of axillary-axillary artery bypass grafting, and a review of the current modalities of surgical correction for symptomatic subclavian occlusive disease form the basis for this report.

Case Reports

Case 1. A 55-year-old male was referred to this institution with a four-day history of rest pain in the right hand. He had sustained four previous myocardial infarctions and had chronic atrial fibrillation. He gave a history of frequent incapacitating episodes of dizziness as well as claudication of the left arm for the past five years. Physical examination revealed a cool, cyanotic right hand and absent right arm pulses. He was also noted to have diminished pulses in his left arm with a blood pressure of 80/60 mm Hg in his left arm compared to a blood pressure of 150/90 mm Hg in his leg. He was taken immediately to surgery where a successful right brachial artery embolectomy was performed.

After recovery from embolectomy, angiography was performed and revealed complete occulsion of the proximal left subclavian artery, complete occlusion of the left common, internal and external carotid arteries, and retrograde flow in the left vertebral artery filling the distal left subclavian artery. An axillary-axillary artery bypass was performed using a 6 mm knitted Dacron graft. A wound hematoma required evacuation on the evening of surgery. He has been followed for three months postoperatively and has noted no episodes of dizziness or left arm claudication. He has maintained excellent graft and arm pulses with equal arm blood pressures. Pre and postoperative arteriograms are shown in Figs. 1a-c.

Case 2. A 47-year-old female was referred to this institution with claudication and rest pain of the left hand. Physical examination revealed a cool cyanotic left hand. The tip of the left index finger was insensitive and appeared pregangrenous. There were markedly diminished pulses in the left arm and there was a 50 mm Hg difference in systolic blood pressure between her arms. Angiography demonstrated near complete occlusion of the proximal left subclavian artery. The impending tissue loss prompted immediate surgical revascularization and an axillary-axillary artery bypass was performed using an autogenous saphenous vein graft.

Postoperatively, the patient has maintained excellent graft and left arm pulses with equalization of arm blood pressures and she has had no further pain for the 12 months she has been followed since surgery.

Case 3. A 50-year-old male entered this institution in mild congestive heart failure complaining of frequent episodes of dizziness associated with bilateral amaurosis fugax. Physical examination revealed diminished left arm pulses and the systolic blood pressure in the left arm was 60 mm Hg lower than that in the right arm. His congestive heart failure rapidly responded to treatment while the episodes of dizziness and blindness increased in frequency and severity.

Angiography revealed a small ulcerated plaque at the left common

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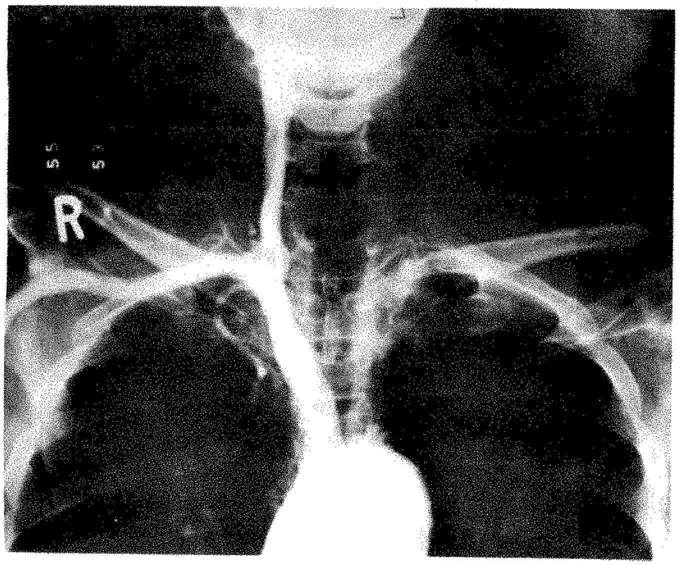

FIG. 1a. Preoperative aortic arch arteriogram showing total occlusion of the left common carotid and subclavian arteries. The innominate artery and right subclavian appear normal.

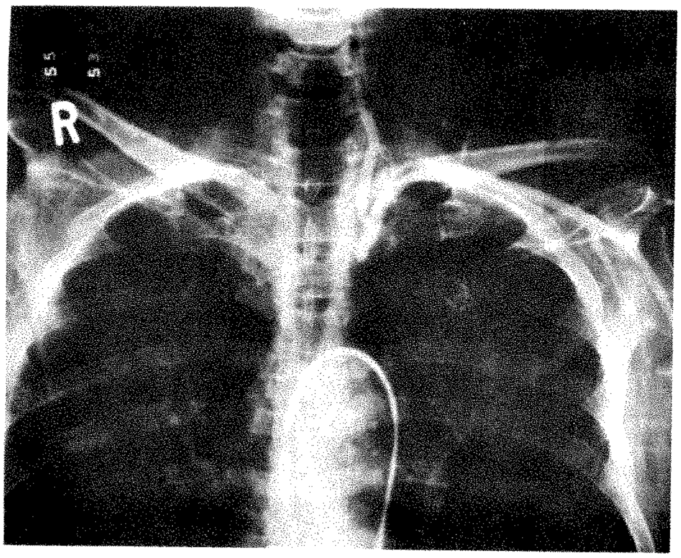

FIG. 1b. Preoperative aortic arch arteriogram late phase showing filling of the left subclavian artery from retrograde left vertebral artery flow.

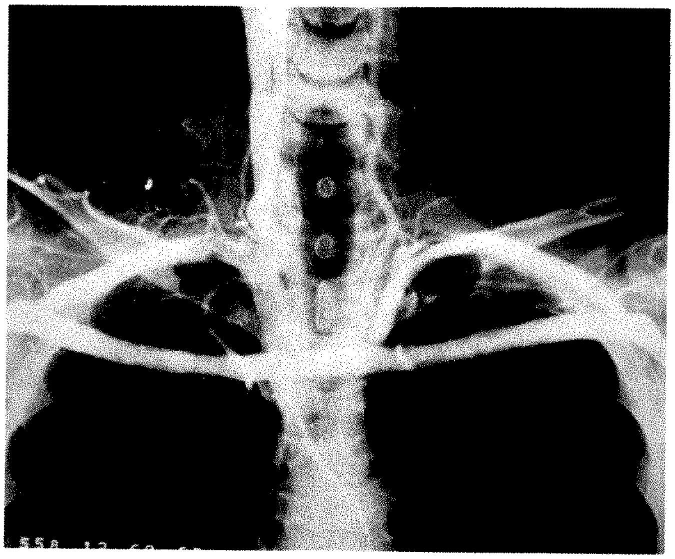

FIG. 1c. Postoperative arteriogram showing patent axillary-axillary graft with antegrade filling of the left vertebral artery.

carotid bifurcation, bilateral narrowing of the intracranial carotid arteries, occlusion of the proximal left subclavian artery and retrograde flow through the left vertebral artery into the distal left subclavian artery.

The patient sustained a right sided hemiparesis the day after angiography. Three weeks later he underwent left carotid endarterectomy and removal of the ulcerated plaque. Convalescence from surgery was uneventful until the twelfth postoperative day at which time he experienced dizziness, dysarthria, worsening of his right hemiparesis and left hemiparesis. Over a four-hour period he became unresponsive to anything other than noxious stimulation. The patient was taken to surgery with the diagnosis of an impending posterior fossa infarction. An axillary-axillary artery bypass was performed under local anesthesia using a 6 mm knitted Dacron graft. The immediate response to surgery was dramatic. The patient regained consciousness, lost all signs of the left hemiparesis and had return of his cranial nerve function. He has been followed for 15 months and has no further episodes of dizziness and has maintained excellent graft and arm pulses as well as equal arm blood pressure. His right hemiparesis has improved slightly. Postoperative angiography showed a patent axillary-axillary artery graft.

Case 4. A 48-year-old institutionalized psychotic male entered this hospital complaining of increasing claudication of his left arm and dizziness with exertion. On physical examination he was noted to have a cool left hand with diminished pulses in his left arm and a 40 mm Hg difference in systolic blood pressure between his arms. Angiography showed occlusion of the proximal left subclavian artery and an independent origin of the left vertebral artery from the aortic arch. The carotid arteries were free of disease.

An axillary-axillary artery bypass was constructed using an 8 mm knitted Dacron graft. He became asymptomatic with excellent left arm pulses and equal arm blood pressures. Routine postoperative angiography showed a widely patent graft.

Eight months postoperatively, the patient noted a cool left hand after sleeping on his left side. Examination revealed an absence of the graft pulse. A graft thrombectomy was performed with the removal of a red thrombus and re-establishment of flow. The mean graft flow was measured at 300 ml/min. Since surgery, the patient has remained asymptomatic and again has excellent left arm pulses and equal arm blood pressures.

Case 5. A 64-year-old male presented to this institution complaining of frequent episodes of dizziness associated with transient bilateral blindness. Three years earlier he had undergone a right carotid endarterectomy and an aortofemoral bypass graft. He had sustained two myocardial infarctions in the recent past and had moderately severe angina pectoris requiring nitroglycerine for relief. Physical examination showed decreased left arm pulses with a 40 mm Hg systolic blood pressure difference between his arms. He had a soft right carotid bruit and a surgical scar on the right side of his neck.

Angiography showed occlusion of the left internal carotid artery and right vertebral artery, complete occlusion of the proximal left subclavian artery and retrograde flow in the left vertebral artery. The right carotid artery failed to demonstrate a significant lesion.

An axillary-axillary artery bypass was performed using an 8 mm knitted Dacron graft. He has been followed 21 months since surgery and has remained asymptomatic. He maintains excellent graft and arm pulses and equal arm blood pressures.

Case 6. A 52-year-old male entered this institution complaining of episodes of dizziness associated with an unsteady gait and blurring of vision. He also noted right arm claudication. Physical examination revealed diminished pulses in the right arm with a systolic blood pressure differential of 40 mm Hg between his right and left arms. Angiography showed complete occlusion of the right subclavian artery with retrograde flow in the right vertebral artery. The right vertebral artery was stenotic at its subclavian origin. The carotid arteries were free of disease.

An axillary-axillary artery bypass was performed using a 6 mm knitted Dacron graft. Mean graft flow was measured at 275 ml/min. Postoperatively the pulses and blood pressure in his right arm have remained normal and he has been totally relieved of the right arm claudication. He noted parasthesias in the distribution of the left median nerve for several weeks after surgery, following which the symptoms totally resolved. The patient has been followed for eight months since surgery without any further symptoms of unsteady gait or blurring of vision.

Operative Technique

Axillary-axillary artery bypass is performed through bilateral 6 cm incisions placed over the delto-pectoral grooves. The fibers of the pectoralis major are separated exposing the attachment of the pectoralis minor muscle to the coracoid process. The insertion of this muscle is transected exposing the axillary artery, the axillary vein and the brachial plexus. A small segment of the axillary artery is exposed by carefully retracting the surrounding structures, taking care not to traumatize the cords of the brachial plexus. Longitudinal arteriotomies are then made after systemic heparinization, and the anastomoses are carried out using 5–0 synthetic cardiovascular suture material in a running fashion. A previously preclotted 6 or 8 mm Dacron graft or an autogenous reversed saphenous vein segment is placed beneath the pectoralis major muscles and anterior to the sternum through a tunnel constructed prior to heparinization. The ends of the graft are fashioned to make approximately a 30° angle anastomosis with the arteries. The pectoralis minor muscle is not re-attached and subcutaneous tissues and skin are closed without drains. Using a two-team approach operative time is usually under one hour. Local anesthesia has been used, but light general anesthesia is preferred. A diagrammatic representation of the surgical procedure is shown in Fig. 2.

Discussion

Subclavian revascularization may be indicated either for arm ischemia or for relief of posterior fossa neurologic ischemic symptoms associated with reversal of flow in the ipsilateral vertebral artery, the subclavian steal syndrome. A variety of surgical procedures have been proposed. Direct revascularization through a thoracotomy can produce significant morbidity, at times approaching 50%.[3] Extrathoracic approaches have been utilized and have enjoyed a much lower morbidity. The carotid-subclavian bypass has been used widely, although there remains considerable controversy concerning the possible development of a vascular "steal" from the ipsilateral carotid artery following this procedure.[2,6] Other possible objections to this procedure include the necessity of clamping the donor carotid artery while the proximal anastomosis is being performed, cerebral embolization from the carotid graft suture line, and stenosis of the carotid graft by kinking with neck motion. Direct carotid-subclavian anastomosis without the use of a graft has been employed and may have the same problems as the carotid-subclavian bypass with the exception of graft kinking. Blaisdell[1] reports a 4% incidence of central nervous system complications after carotid-subclavian bypass.

Another approach to symptomatic proximal subclavian

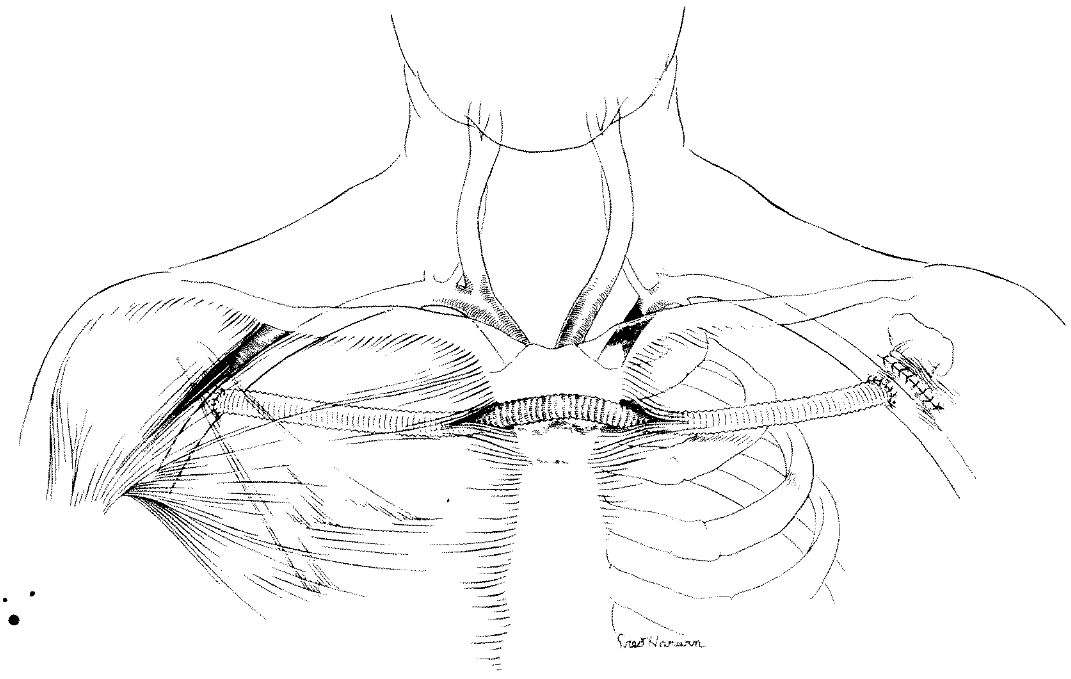

FIG. 2. Diagrammatic representation of our method of placement of the axillary-axillary graft.

artery occlusive disease has been the subclavian-subclavian artery bypass, which does not require opening the pleura or manipulation of the carotid artery.[4,5] The morbidity following this procedure has been reported as low, although the dangers of entering the pleura, injury to the phrenic nerve, injury to the thoracic duct, and graft occlusion with neck motion are present. Two reports describe femoral-axillary bypass for symptomatic subclavian and innominate artery stenosis.[9,13] The length of this bypass and the vulnerable position it must take on the body surface make its routine use impractical. Vertebral artery ligation has been proposed to eliminate the retrograde vertebral flow in the subclavian steal syndrome, but the results from this procedure have not been uniformly successful. It is generally agreed that revascularization with the re-establishment of antegrade flow in the vertebral artery is the best approach.

The axillary-axillary artery bypass procedure is technically easy to perform, can be done rapidly, and has not been associated with any significant morbidity. None of our patients has developed any new central nervous system symptoms, all are free of arm claudication and none has any restriction of arm motion or significant cosmetic defect incident to surgery. One patient experienced a graft thrombosis at eight months thought to be secondary to graft kinking during sleep in an unusual position. This was promptly corrected with thrombectomy and the graft has remained patent to the present. A second patient developed a wound hematoma on the day of surgery requiring evacuation and a third patient developed mild parasthesias in the median nerve distribution of his right arm likely caused by retraction of this nerve cord at surgery. The parasthesias soon disappeared and he has maintained normal hand function.

The construction of an axillary-axillary bypass increases blood flow in the donor subclavian-axillary artery by about 300 ml/min. It is obviously essential that there be no significant stenosis present in the donor vessels. Complet angiographic visualization of the donor vessels should b performed preoperatively, as was done in all patient described in this report. In the absence of donor stenosi there appears to be little likelihood of developing a vascula steal from the donor arm.

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The Role of Bile in Antral Mucosal Disruption During Hemorrhagic Shock

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The stress ulcers that occur in shocked dogs are averted by pyloric cross-clamping prior to shock. These experiments studied the role of bile reflux in the pathogenesis of stress ulcers in the shocked dog. Two and one-half hours of hemorrhagic shock in dogs with acute antral pouches isolated from the duodenum did not alter antral mucosal integrity as measured by gastric mucosal volume and ionic flux rates despite a fall in transgastric potential difference (PD) indicating mucosal injury (−33.5 ± 1.7 m Volts vs −12.8 ± 2.0, $p < 0.01$). Similarly 4½ hours of shock did not alter mucosal integrity when the pylorus was cross-clamped during shock (PD −59.8 ± 1.8 mV vs −42.5 ± 7.0, $p = 0.05$). In contrast, 4½ hours of shock in dogs in whom the pylorus was open resulted in increased hydrogen ion back diffusion (−106.3 ± 21.5 μEq vs −300.5 ± 63.1, $p < 0.01$, PD −56.8 ± 3.6 mV vs −24.3 ± 3.4, $p < 0.01$). The concentration of bile acids refluxed into the stomach during unmodified shock (8.45 ± 3.92 mM) exceeds that necessary to disrupt the gastric mucosal barrier. These data suggest that increased hydrogen ion back diffusion initiated by refluxed bile plays an important role in the pathogenesis of gastric stress ulcers in the shocked dog.

EXPERIMENTAL EVIDENCE suggests that bile, refluxed into the stomach from the duodenum, is an essential component in the pathogenesis of stress ulcers in dogs subjected to hemorrhagic shock and then resuscitated by infusion of their shed blood.[6,7] Topically applied bile disrupts the gastric mucosal barrier resulting in increased hydrogen ion loss from the gastric lumen into the mucosa (back diffusion).[3] These data imply that increased hydrogen ion back diffusion is also an essential preceding component of stress ulcer formation in the shocked dog model.

There is conflicting data as to whether hemorrhagic shock alters the gastric mucosal permeability in the absence of bile reflux. Ritchie and Fischer observed increased hydrogen ion back diffusion in isolated corporal pouches during hemorrhagic shock.[12] In contrast, Moody and Aldrete did not observe increased hydrogen ion back diffusion in isolated corporal chambers after shorter periods of shock.[11] Similarly DenBesten and Hamza did not observe increased hydrogen ion back diffusion during hemorrhagic shock when duodenal reflux was prevented by pyloric cross-clamping.[5] Their study did not determine gastric permeability when the pylorus was not cross-clamped prior to shock. There are no reports on the intrinsic response of the canine antrum to hemorrhagic shock, nor has the bile reflux that occurs during hemorrhagic shock been quantified. The experiments presented here determined the concentration of bile refluxed into the stomach during hemorrhagic shock in the dog and determined the response of the antral mucosa to hemorrhagic shock both with and without the duodenal reflux.

Experimental Design and Methods

Canine antral mucosal integrity was tested by measuring the net transmucosal flux rates of hydrogen, sodium, chloride and potassium ions, by measuring net volume flux rates, and by measuring the transgastric electric potential difference in acute antral pouches. These studies were performed: 1) under resting conditions; 2) after 2½ hours of hemorrhagic shock, in isolated antral pouches; and 3) after 4½ hours of hemorrhagic shock, with and without prior pyloric cross-clamping to prevent duodenal reflux.

Fasted adult mongrel dogs of either sex weighing 15–25 kg were used. They were lightly anesthetized with intravenous sodium thiopental, intubated and allowed to spontaneously breathe room air. Transgastric electrical potential difference (PD) was measured between the gastric lumen and the venous blood using #260 polyethylene

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tubing electrolyte bridges filled with saturated potassium chloride in a 4% agar gel. The venous electrolyte bridge was placed into the inferior vena cava via a femoral vein. The luminal electrolyte bridge was placed via antrotomy except in experiment III where it was placed via an indwelling orogastric tube. The ends of these electrolyte bridges were placed in separate beakers filled with saturated potassium chloride and connected to a Keithley Instruments 602 potentiometer via Beckmann instrument 39402 calomel electrodes. Arterial blood pressure was monitored, arterial samples drawn, and hemorrhage accomplished via indwelling femoral arterial cannulae. Pouches were constructed prior to shock for the anesthesia controls experiment and for experiment II. The pouches used in experiment III were constructed after 4½ hours of shock. Pouches were constructed via midline abdominal incisions. The antrum was catheterized via the duodenum and the catheter secured in the pyloric channel with an umbilical tape tied around the antrum just proximal to the pylorus. A Payr clamp was then placed across the midantrum to complete the pouch. The umbilical tape and Payr clamp were carefully placed to avoid injury to the antral blood supply.

The pouch pH at the beginning of each experiment was 1.8, the pH of the test and wash solutions. Pouch pH was not determined at the termination of shock. During unmodified hemorrhagic shock in dogs the gastric luminal pH is significantly greater, presumably because of reflux of alkaline duodenal chyme, than in dogs in whom the pylorus is cross-clamped prior to shock.[6] The trauma imposed by irrigation and aspiration of the flux solutions resulted in patchy areas of erythema often associated with superficial erosions. The dogs were sacrificed at the termination of the experiments.

The effects of pouch distention upon ionic fluxes were minimized by using small instilled test solution volumes (less than 20 ml) and by using the same instilled volumes for each paired experiment. Subsequent studies have shown that the intraluminal pouch pressures produced using these instilled volumes range 6–16 cm of water. Flux studies were performed for 30 minutes using isotonic test solution of 80 mM HCl and 80 mM NaCl with 4 mg% phenol red (PSP) as a nonabsorbable volume marker. Initial pouch volume (IPV) and final pouch volume (FPV) were calculated from PSP dilutions using the following equations: $\text{IPV} = (\text{Volume A} \times \text{PSP}_\text{A}/\text{PSP}_\text{B}) - \text{Sample B}$. $\text{FPV} = \text{IPV} \times \text{PSP}_\text{B}/\text{PSP}_\text{C}$. A = instilled test solution. B = initial test solution after mixing of instilled test solution with residual volume. Sample B = sample of initial test solution removed for analysis. C = test solution at termination of flux period. Initial and final ionic contents were calculated in multiplying the ionic concentrations initially and at the termination of the flux period times the IPV and FPV respectively. Net volume flux equals the IPV minus the FPV. Net ionic flux equals initial ionic content minus final ionic content. (Positive flux = gain into pouch, negative flux = loss from pouch.) Pouch surface area was determined by planimetry after the mucosa was dissected from the muscular antrum.

Arterial blood samples were drawn at the midpoint of each flux period. Blood gases and pH were determined on a Radiometer blood gas analyzer. Sodium and potassium concentrations were determined on an Instrumentation Laboratories flame photometer. Chloride concentrations were determined on a Buchler-Cotlove chloridometer. Hydrogen ion concentrations were determined by titration to pH 7 with a 0.01 NaOH. PSP concentrations were determined after removal of blood and bile contaminants.[20] Lactate determinations were made from Boehringer-Mannheim kits. Total bile acid determinations were performed by the steroid dehydrogenase method of Thomas[16] which is based upon that of Hurlock and Talalay.[8] The method is similar to that published by Turnburg and Anthony-Mote[17] except that hydrazine is used to increase the steroid oxidation rate by virtue of the ketone binding capacity of hydrazine. Comparisons between the control and experimental flux data of experiment I and II and the control and experimental PD data of all studies were made using the Student t test for small paired samples. Comparisons of the experimental data from experiment III were performed using the Student t test for small unpaired samples.

Experiment I

Anesthetic Controls (Five Dogs)

After creation of an antral pouch and a 30–60 minute period of stabilization, a control flux study was performed. The dog was then maintained on sodium thiopental anesthesia for five hours prior to an experimental flux study.

Experiment II

2½ hours of Hemorrhagic Shock, Isolated Antral Pouches

This experiment, using acute antral pouches, duplicates the hemorrhagic shock protocol of Ritchie and Fischer who studied chronic corporal pouches.[12] An antral pouch was constructed, 30–60 minutes were allowed for stabilization, and a control flux was performed. The dogs were then shocked by arterial hemorrhage over 30 minutes to a mean arterial blood pressure to 50 mm Hg and maintained at this level. After 2½ hours of shock an experimental flux was performed.

Experiment III

4½ Hours of Hemorrhagic Shock. With and Without Pyloric Clamping to Prevent Duodenal Reflux

This experiment duplicates the experimental conditions of Guilbert, Bounous and Gurd who demonstrated that gastric stress ulcers produced in the shocked dog could be averted by cross-clamping the pylorous prior to hemorrhagic shock.[6] In the pyloric clamped experiment the pylorus was cross-clamped with an atraumatic vascular clamp prior to hemorrhage. In the pylorus open experiment the pylorus was dissected, but not cross-clamped, prior to hemorrhage. Prior to hemorrhage, the stomach was lavaged with test solution without PSP and emptied via a #16 orogastric tube. The orogastric tube was left in place, not on suction, throughout the experiment. After stabilization the dogs were shocked to a mean arterial blood pressure of 40 mm Hg over 30 minutes and maintained at this level. After 4½ hours of shock, an antral pouch was constructed and an experimental flux performed.

TABLE 1. *Net Antral Ionic and Volume Flux Rates and Transgastric Potential Differences Before and After 2½ Hours of Hemorrhagic Shock (Isolated Antral Pouches)**

	Control	Shock	Probability
Net Volume† (ml)	+5.5 ± 1.1	+3.5 ± 0.9	NS
Net H‡ (μEq)	−106.3 ± 21.5	−93.9 ± 20.6	NS
Net Na† (μEq)	+769.9 ± 148.8	+520.8 ± 136.9	NS
Net K† (μEq)	+30.6 ± 5.8	+36.8 ± 2.4	NS
Net Cl† (μEq)	+799.6 ± 144.2	+517.5 ± 174.9	NS
Potential Difference (m Volts)	−33.5 ± 1.7	−12.8 ± 2.0	<0.01

Flux rate ± SEM/30 min./100 cm² mucosa.
* n = 5.
† Pouch gain.
‡ Pouch loss.

Experiment IV

Bile Reflux During 4½ Hours of Hemorrhagic Shock

This experiment duplicated the pylorus open experiment. After 4½ hours of hemorrhagic shock the pylorus and mid-antrum were cross-clamped and the gastric juice in the antrum and proximal stomach aspirated.

Experimental Results

I. Anesthesia Controls

No changes occurred in the transgastric electric potential difference, the net ionic or volume flux rates, arterial pH, Pco_2, HCT or lactate concentrations after six hours of anesthesia.

II. 2½ Hours of Hemorrhagic Shock, Isolated Antral Pouches (Table 1)

The net ionic and net volume flux rates were not altered by 2½ hours of hemorrhagic shock despite a significant decrease in potential difference indicative of mucosal injury. Increased hydrogen ion back diffusion did not occur. This finding is in contrast with an earlier study in which increased hydrogen ion back diffusion was found in isolated corporal pouches after 2½ hours of hemorrhagic shock.[11]

Significant arterial acidosis (pH 7.2 ± 0.03 vs 7.41 ± 0.03 $p < 0.001$), hyperkalemia (K 6.0 ± 0.1 vs 4.1 ± 0.4, $p < 0.001$) and lactic acidosis (141.2 ± 7.1 vs 59.8 ± 8.3, $p < 0.001$) developed during hemorrhagic shock.

III. 4½ Hours of Hemorrhagic Shock

A. *Pylorus Clamped Experiment (Table 2).* Net ionic and net volume flux rates were not altered as compared to the unpaired controls of experiment II. Increased hydrogen ion back diffusion did not occur. The PD decreased significantly during the 4½ hours of shock (P. = .05).

B. *Pylorus Open Experiment (Table 2).* Hydrogen ion back diffusion increased significantly after 4½ hours of hemorrhagic shock, as compared to the unpaired controls of experiment II, ($P < 0.01$). Similarly there was greater hydrogen ion back diffusion (P. < 0.05) as compared to the pylorus clamped group. There were no alterations in the net ionic or net volume flux rates as compared to the controls of experiment II or to the pylorus clamped group, and the PD decreased significantly (P. < 0.01). The increased hydrogen ion back diffusion without an associated increase in sodium influx and the other flux changes classically described with gastric mucosal barrier disruption is similar to our findings in corporal pouches in shocked dogs.[11] It has been hypothesized that these findings are consistent with passive ionic movement across the gastric mucosa in response to a decrease in transgastric potential difference.[11]

IV. Bile Reflux During 4½ Hours of Hemorrhagic Shock (Table 3)

Gastric juice and refluxed bile pooled in the proximal stomach of these supine dogs. In the proximal stomach, the mean concentration of bile acid was 8.45 mM. The volume of gastric juice in the antrum was insufficient for analysis in three dogs. The mean antral bile acid concentration in the remaining four dogs was 1.02 mM.

Discussion

Gastric lesions similar in appearance to stress ulcers occur in dogs subjected to hemorrhagic shock and then resuscitated with their shed blood. These antral and corporal lesions are averted by preventing duodenal reflux by cross-clamping the pylorus prior to shock.[6] It is believed that bile induces stress ulcers in the shocked dog by increasing mucosal hydrogen ion back diffusion and that these hydrogen ions acting in consort with ischemia initiate mucosal destruction (perhaps by exceeding the intracellular buffering capability of these ischemic cells and by the release of tissue histamine).

Acid seems an essential ingredient in the experimental

TABLE 2. *Net Antral Ionic and Volume Flux Rates and Transgastric Potential Differences After 4½ Hours of Hemorrhagic Shock**

	Control (Experiment II)	Pylorus Cross-clamped	Probability	Pylorus Open		Probability
Net Volume† (ml)	+5.5 ± 1.1	+4.7 ± 1.1	NS	+5.3 ± 0.4		NS
Net H‡ (μEq)	−106.3 ± 21.5	−87.4 ± 24.9	NS	−300.5 ± 63.1		<0.01
Net Na† (μEq)	+769.9 ± 148.8	+540.4 ± 126.2	NS	+678.7 ± 28.7		NS
Net K† (μEq)	+30.6 ± 5.8	+60.7 ± 21.7	NS	+53.7 ± 28.7		NS
Net Cl† (μEq)	+799.6 ± 144.2	+565.4 ± 135.4	NS	+323.7 ± 48.3		NS
	Control	Shock	Probability	Control	Shock	Probability
Potential Difference (m Volts)	−59.8 ± 1.8	−42.5 ± 7.0	0.05	−56.8 ± 3.6	−24.3 ± 3.4	<0.01

Flux rate ± SEM/30 min/100 cm² mucosa.
* n = 4.
† Pouch gain.
‡ Pouch loss.

models of stress ulcer formation. Reduction of the luminal acid eliminates or sharply reduces the incidence of stress ulcers in these models.[15] Stress ulcers do not occur in vagotomized dogs subjected to hemorrhagic shock, in whom the pylorus has been cross-clamped, despite the instillation of bile into the stomach but do occur of both bile and acid and instilled into the stomach prior to shock,[14] and the back diffusion prompted by bile is inversely proportional to gastric luminal pH.[2] Further data implying that acid-peptic digestion is intimately related to the formation of stress ulcers and/or other forms of acute erosive gastritis are: 1) bile disruption of the gastric mucosal barrier in dogs causes gastrin release;[1] 2) alcohol and acid disruption of the gastric mucosal barrier in dogs causes pepsin release;[10] and 3) increased hydrogen ion back diffusion is accompanied by histamine release which presumably increases acid secretion and hence further increases hydrogen ion back diffusion.[16]

Bile appears to be the constituent of duodenal chyme injurious to the gastric mucosa in shocked dogs. The exclusion of pancreatic juice reflux is not protective and stress ulcers occur when the pylorus is cross-clamped but bile is added to the stomach prior to hemorrhagic shock.[7] Similarly, cholestyramine (a basic anionic exchange resin that binds bile) instilled into the stomach of shocked dogs, prevents stress ulceration.[19] Topically applied bile disrupts the gastric mucosal barrier resulting in an increase in hydrogen ion back diffusion. In the dog antrum bile increases hydrogen ion back diffusion 2.4–3.5 fold,[18] and the dog antrum is more sensitive to the topical application of bile than the gastric corpus.[13] Increased hydrogen ion back diffusion resulting from the intragastric instillation of bile does not, however, trigger stress ulcer formation unless this circumstance is combined with intrinsic mucosal injury produced by hemorrhagic shock. Hemorrhagic shock does not increase hydrogen ion back diffusion in the antrum isolated from the duodenum (see experimental results), nor does hemorrhagic shock further increase the hydrogen ion back diffusion that occurs in normotensive dogs after acid and bile instillation into the distally occluded stomach.[5] The mean concentration of bile acids recovered from proximal stomach in these experiments (8.45 mM) exceeds the concentrations needed to disrupt the gastric mucosal barrier and to increase hydrogen ion back diffusion in both dogs (2.0 mM)[4] and in man (5.0 mM).[8]

TABLE 3. *Bile Acid Concentrations (mM) in Stomach After 4½ Hours of Hemorrhagic Shock*

Dog. No.	Antrum	Proximal Stomach
1	0	0
2	0.1	0.6
3	2.6	12.6
4	1.4	12.6
5	—	28.6
6	—	2.8
7	—	2.0
Mean	1.02	8.45
SEM	0.55	3.92

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Clinical Infections Detected by ^{67}Ga Scanning

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Gallium-67 was utilized in 34 patients suffering from clinically demonstrable infections. The isotope was able to localize infections in soft tissue, bones, and some areas of the abdomen. Its utilization in the diagnosis of pelvic inflammatory disease is complicated by the fact that the isotope is secreted into the bowel and obscures the area. This isotope is ideal for the diagnosis of acute and/or chronic inflammation of bone secondary to open reduction of fractures, and may also be of use in the diagnosis of primary osteomyelitis.

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THE DIAGNOSIS of deep-seated purulent collections is still a clinical dilemma because the development of new diagnostic modalities has remained relatively static throughout the last decade. Thus, we continue to rely heavily on physical examination of areas that are often anatomically remote. In an effort to improve our diagnostic capabilities, we have attempted to develop methodology geared to tagging the components of an abscess cavity with radioactive compounds, rendering it radioactive and amenable to scans. In the past, we reported success in localizing experimental abscesses in rabbits, using ^{51}Cr labeled autologous leukocytes, followed by anterior scannings.[4] This procedure, however, did not prove practical for clinical use due to technical difficulties in obtaining a pure, viable leukocyte specimen for labeling which was sterile and noncontaminated with red cells. Nevertheless, those experimental attempts did prove the feasibility of rendering an abscess radioactive.

Gallium-67 citrate has been utilized in localizing and staging Hodgkin's disease, reticulum cell sarcoma, lymphosarcoma and squamous cell carcinoma of the lungs.[7,8,13] Recently, ^{67}Ga has been reported to be successful in tagging abscesses in experimental animals as well as in clinical trials. However, it has been used only in a small series of patients.[6,9,11,12]

The purpose of this study was to evaluate the usefulness of ^{67}Ga citrate scanning in the detection of clinical purulent collections. Most of our patient population had abscesses easily detected by routine clinical means. This allowed us to observe the progress of the isotope into an obviously infected area and to understand better the natural history of some clinical infections. It was our hope that from this study additional indications for the utilization of ^{67}Ga would become obvious. In some cases, nonsuspected foci of infection became apparent in the scan. The study also demonstrated the usefulness of this method in detecting chronic osteomyelitis.

Methods

Thirty six patients with clinically suspected purulent collections were selected from the General Surgery, Orthopedics, Obstetrics and Gynecology, and Medical Departments at the Queens Hospital Center. Documentation of infection was based on the presence of drainage, fever, palpable abscesses, high leukocyte counts and operative findings either alone or in combination. Control studies of clean wounds were provided by postoperative patients with herniorrhaphies and patients who underwent closed or open reduction of fractures with and without internal fixation.

The conditions of the study were thoroughly explained to all patients and voluntary written consent was obtained. Gallium-67 citrate (2.5–3.0 mCi), supplied by Diagnostic Isotopes of New Jersey, was injected into the antecubital vein and patients were scanned 24 and 48 hours later on either a Picker Magna Scanner (window openings: upper, 330, lower 80 and 12.5 cm high energy collimator) or a General Electric Nuclear Scanner WBS 220 (window

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openings: upper 310, lower 70, center 195 collimator VC3). The latter instrument displays the image as either black and white photoscans or in color on a videoscreen which can then be photographed. In addition, all scanning information is recorded on magnetic tape. This allowed us later playback and better data interpretation. Most patients with abdominal purulent collections were prepared for scanning by cleansing enemas and emptying their bladders, since ^{67}Ga is excreted into the bowel and by the kidneys. Those patients suffering from pelvic inflammatory disease were not given enemas because of the danger of spreading the infection.

Results

A total of 34 patients was injected and scanned without local or general reactions to the ^{67}Ga citrate. The results of the scannings are tabulated in Table 1. Two patients with superficial postoperative wound infections were scanned; one was drained and the other observed. In the latter, treated with antibiotics, we were able to follow the resolution of the infection by repeated scanning. Controls for postoperative wound infections were provided by six patients who underwent uncomplicated elective inguinal herniorrhaphies and who demonstrated negative scans.

Five patients with clinical manifestations of pelvic inflammatory disease were studied. The results of the scan were difficult to interpret because of the presence of overlying bowel containing radioactive feces. The scans were not helpful in these patients. Furthermore, as they were treated with antibiotics and not subjected to laparotomy, the diagnosis was difficult to confirm and correlation could not be established. There was one false negative result in a patient harboring a pelvic abscess which was later drained. This collection did not reveal itself on the scan and the pus obtained was found to be nonradioactive. In one patient with generalized peritonitis we observed uniform pickup over the entire abdomen.

Bone infections were easily detected by this method and areas of pickup coincided with zones of known osteomyelitis. Some of these patients with chronic bone infection had originally suffered from acute hematogeneous osteomyelitis. In other patients the infections were secondary to either compound fractures or infected open reductions of fractures with internal fixation. Some areas in which the diagnosis of osteomyelitis was difficult to establish by clinical means but which became radioactive were drained and yielded pus, thus confirming the result of the scanning. In contrast, those patients who underwent closed reduction, with or without internal fixation, and did not become infected, failed to develop positive scans and were utilized as comparative studies (Figs. 1 and 2).

Soft tissue abscesses, usually easily diagnosed, were well detected by this method in seven patients. However, in some, ^{67}Ga revealed, additionally, areas of unsuspected infection. One such patient was a heroin addict with a massively swollen forearm in which an area contained an obvious abscess. The scan revealed another purulent collection in the distal forearm which also required drainage.

Discussion

These studies confirm the impression of other authors that Gallium-67 may be a helpful tool in the diagnosis of clinical purulent collections. Previous reports had presented small series of patients in which this isotope was utilized, without significant clarification concerning indications for its use.[6,9,10,12]

Postoperative wound infections were easily diagnosed by the uptake of radioactive ^{67}Ga with diminution of the radioactivity as the infected area was drained. Controls for comparison with these patients were obtained by studying clean, elective surgical wounds which did not become clinically infected and which did not pick up the isotope. We did not attempt to use this method of diagnosis for patients with acute appendicitis because as soon as the diagnosis was made by clinical examination, they were operated upon to avoid unnecessary delays.

Soft tissue abscesses were remarkably easy to scan and detect by this method. This type of inflammation is diagnosed by simple physical examination. Nevertheless, in one of our patients addicted to heroin, examination of the extremity was extremely difficult to evaluate because of preexisting nodularities resembling abscess collections. An area otherwise clinically undiagnosed was proven to harbor pus by the ^{67}Ga scan. Other soft tissue inflammatory processes, like carbuncles, clearly showed isotope pickup.

Gallium-67 scan proved to be a most useful tool in detecting bone infection. Simple or compound fractures, treated by open reduction, became rapidly radioactive if infection occurred. Similarly, patients suffering from active chronic osteomyelitis also revealed areas of heavy isotope uptake. Our controls were provided by patients who underwent closed or open reductions of fractures without evidence of infection. Gallium-67 may be ideal for detecting very early areas of primary osteomyelitis and thus indicate the need for antibiotic therapy before local and systemic spread of the infection.

We had hoped to utilize this method to detect subphrenic purulent collections, but during the term of our study, no patient presented such pathology. The high mortality and morbidity of undrained subphrenic collections reflects the need for an accurate localizing diagnostic test. However, in this area, certain limitations in technique do exist since ^{67}Ga accumulates in the reticuloendothelial system of the liver. Because of this propensity, the diagnosis of subphrenic abscess by this isotope will undoubtedly be difficult. The whole liver can become radioactive, overshadowing the lesser pickup by the abscess. Alternate techniques have been utilized by Littenberg,[11] scanning the liver with ^{99}TcS coloid to reveal a filling defect and then rendering this defect radioactive by ^{67}Ga. It is also interesting that Blair[1] has demonstrated in experimental animals that the uptake of ^{67}Ga by the abscess continues to increase with time, while

TABLE 1. *Results of Scanning with ^{67}Ga Citrate*

Patient	Age	Sex	Clinical Diagnosis	Procedure	Location of Infection	Gallium Uptake	Hospital Course
1. J.C.	27	F	CA of cervix	Total hysterectomy	Wound	Positive over wound	Antibiotics, drainage, healing
2. S.D.	28	F	Generalized Peritonitis	Exploratory Laparotomy	Peritoneal Cavity	Positive throughout the abdomen	Antibiotics, recovered
3. J.S.	36	M	Gunshot wound of abdomen	Exploratory Laparotomy	Wound	Positive over wound	Antibiotics, drainage, healing
4. Y.B.	24	F	Pelvic inflammatory disease	Observation	Pelvis	Obscured by uptake in colon	Resolution of pelvic mass Pt. discharged
5. D.B.	23	F	Fracture R head of radius	Excision R radial head	Wound	Positive over operated area	I & D, pus radioactive, healed
6. C.F.	92	M	Fracture R femur	Internal fixation	Wound	Positive over wound	I & D, healed
7. J.D.	54	M	Carbuncle of the neck	I & D	Neck	Positive over carbuncle.	Antibiotics, drainage
8. J.L.	63	M	Sigmoid diverticulitis	Exploratory Laparotomy	Pelvis	Positive over pelvis	Antibiotics, recovery
9. E.K.	75	M	Fracture neck R femur	Austin Moore Prosthesis	None	None	Uneventful
10. J.O.	43	M	Chronic osteomyelitis L thigh	I & D	Left femur	Positive over bone	Drainage
11. W.M.	50	M	Chronic osteomyelitis R femur	Saucerization	Right femur	Positive over bone	Antibiotics, drainage
12. S.P.	29	M	Gunshot wound perforating colon	Colostomy, drainage of pelvic abscess	Pelvis	False Negative	Exploration revealed large pelvic abscess, recovery
13. S.S.	21	M	R inguinal hernia	Herniorrhaphy	Control	Negative	Uneventful
14. M.D.	21	M	L inguinal hernia	Herniorrhaphy	Control	Negative	Uneventful
15. L.B.	44	M	Chronic duodenal ulcer	Hemigastrectomy	Wound	Positive over wound	Scans of diminishing intensity in 3 days. Wound was not draine Antibiotics, recovery
16. H.O.	64	M	Fracture R femur	Open reduction, internal fixation	Control	None	Uneventful
17. H.P.	70	F	Fracture L tibia and fibula	Closed reduction. Cast	Control	None	Uneventful
18. E.P.	81	F	Fracture L femur	Open reduction, internal fixation	Control	None	Uneventful
19. J.I.	66	M	Arteriosclerotic gangrene L foot	AK amputation	Control	None	Uneventful
20. J.R.	33	F	PID	Observation	Pelvis	Positive	Diminishing pelvic mass, antibiotics
21. J.P.	48	M	Arteriosclerotic gangrene second L toe	Amputation of toe	Stump	Positive over wound	I & D, healed
22. S.H.	43	M	Fracture L femur	Open reduction, internal fixation	Control	None	Uneventful
23. K.D.	32	F	Prepatellar abscess	I & D	Prepatellar area	Positive	I & D, recovery
24. D.S.	16	F	PID	Observation	Pelvis	Positive, diminishing in subsequent days	Antibiotics, diminish mass
25. R.S.	29	F	Cellulitis L foot	I & D	Left foot	Positive	Antibiotics, resolution
26. R.A.	28	M	Perianal abscess	I & D	Perianal area	Positive over abscess	I & D, recovery
27. A.B.	32	F	PID	Observation	Pelvis	Positive over pelvis diminishing in subsequent days	Antibiotics
28. H.C.	49	F	Compound fracture R tibia, osteomyelitis	Debridement, open reduction internal fixation	Right tibia	Positive over wound	I & D, resolution
29. R.H.	19	F	PID	Antibiotics	Pelvis	Positive, diminishing thru the days	Antibiotics
30. E.R.	22	M	Narcotics addict, subcutaneous abscesses in R & L forearm	I & D	Right & Left forearm	Positive, additional abscesses discovered by scan and drained	Antibiotics
31. E.H.	29	M	Heroin addict, R forearm abscesses	I & D	Right forearm	Positive	Antibiotics, discharged
32. J.M.	28	M	Fracture R femur	Open reduction, internal fixation	Over bone	Positive	I & D
33. R.H.	35	M	Chronic osteomyelitis, R tibia	Bone grafting & internal fixation	Right tibia	Positive over area of operation	I & D on traction
34. R.C.	88	F	Acute colecystitis	Colecystectomy	Liver & Brain	Positive over liver and brain	Discharged after long postoperative course
35. J.R.	81	M	Intertrochanteric Fixation R Hip	Open reduction, internal fixation	None	None	Discharged
36. A.H.	67	F	Old fracture R femur. Followed by aseptic necrosis head of R femur	Open reduction, Internal fixation. AM prothesis.	Infection of head of R femur, not supported by surgical findings.	Negative scan preceeded most recent operation	Discharged

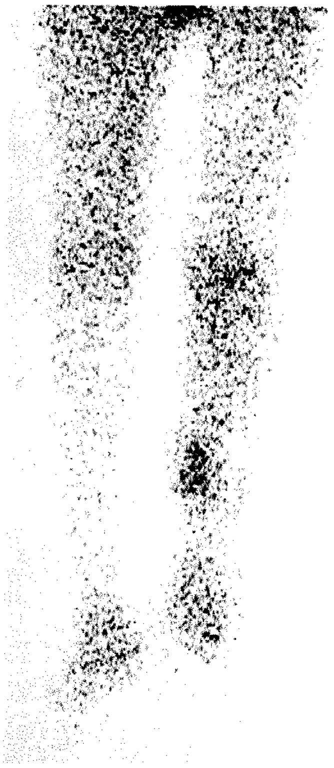

FIG. 1. Posterior scan of patient 33 demonstrating uptake over infected bone.

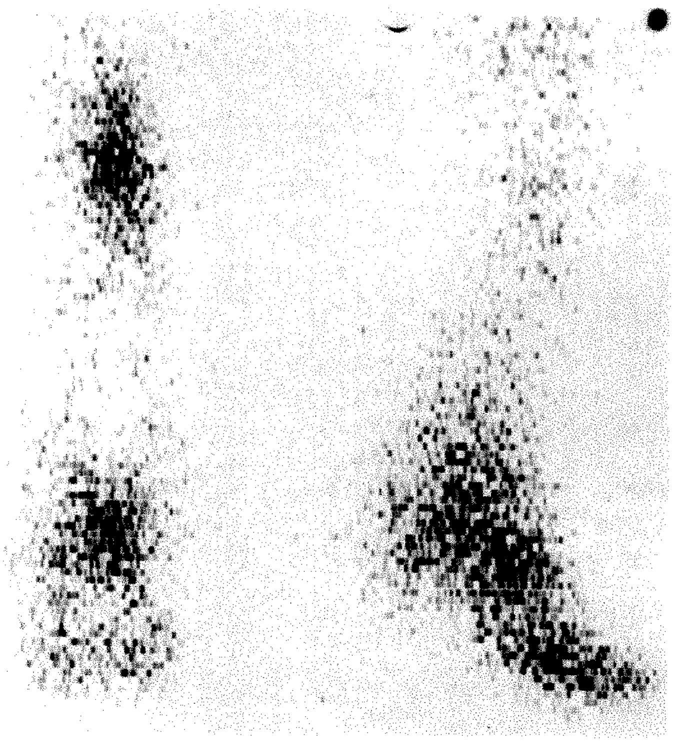

FIG. 2. Posterior scan of patient 28. Uptake is evident over infected fracture site.

this same time factor results in decreasing hepatic radioactivity. These differences in radiokinetics may be significant enough to allow visualization of a subphrenic abscess if the liver eliminates the drug faster than the abscess. We have not been able to confirm such observations in our laboratories. In nonpublished experimental work we have observed that subphrenic abscesses created in dogs became less radioactive than did the liver.[5]

Another important question to be answered deals with determining the ideal time to inject ^{67}Ga in order to visualize abscesses of different ages. Burleson, *et al.* studied the natural history of both intravenously injected gallium and the injection of gallium-labeled leukocytes, demonstrating that both methods clearly tagged abscesses 3–14 days old. They also stated that intravenous ^{67}Ga citrate produced a clear label in abscesses beginning four hours after injection with maximum accumulation in five days. These investigators have also studied the kinetics involved in *in vitro* as well as *in vivo* labeling of rabbit leukocytes with ^{67}Ga. They demonstrated that maximal *in vitro* labeling occurred within one hour with minimal labeling of red cells.[2,3] Gelrud was able to obtain positive scintophotos 1.5 hours postinjection in studies conducted in biogenic and sterile subcutaneous abscesses in the limbs of monkeys.[6] We did not find any difference in the quality of the scans 24 hours postinjection as compared to those obtained 48 hours later. In our experience we were able to observe the resolution of some purulent collections after antibiotic therapy and drainage, and this was manifested by the diminishing uptake in serial scanning.

An additional limitation to this technique relates to the bowel uptake of ^{67}Ga. This area of radioactivity obscures the pelvis during attempts to diagnose pelvic inflammatory pathology. To a great extent, this problem can be alleviated by enemas, but it has been our experience that the bowel continues to secrete isotope, making the interpretation of the test difficult. Furthermore, enemas may be contraindicated in patients suffering from pelvic inflammatory disease.

This system is far from perfect, but it can be a valuable diagnostic test when a decision has to be made concerning surgical exploration for suspected suppuration in a poor risk patient. Its use is limited in patients harboring carcinoma with metastases, as these present to the isotope an area of higher affinity than the one produced by a suspected inflammation.

Gallium-67 may become a valuable tool in the complete evaluation of a patient being studied for the presence or absence of an abscess. This isotope is not, in our opinion, the final answer to the problem but has allowed us to understand better the pathogenesis of suppuration. We believe that it is a step forward in our search for the development of new methods for abscess diagnosis. It is evident from this study that ^{67}Ga will be utilized most efficiently in those areas related to bone infection, as the scanning is not only accurate, but can be easily compared with the normal contralateral limb.

Acknowledgment

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The Operative Cholangiogram:

Its Interpretation, Accuracy and Value in Association with Cholecystectomy

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The value and errors of one method of operative cholangiography were assessed prospectively with the aim of reducing further the incidence of unnecessary explorations of the common bile duct and the occurrence of residual stones. Operative cholangiograms were obtained using a cystic duct cannula in 174 cases, the technical failure rate being 2%. All cases were followed up using intravenous cholangiography where necessary. Of 129 judged normal by the operator, 2 were found to have common bile duct stones—false negative rate 1%. Of 45 judged abnormal by the operator, 10 had negative explorations—false positive rate 6%. Anomalies were discovered in 12% of patients. It is concluded that meticulous technique and accurate interpretation are essential for the best results. The high incidence of anatomical variations present is of interest and this alone emphasises the necessity of carrying out the investigation and the need of experienced interpretation.

RESIDUAL STONES and bile duct injury are two of the most important factors which influence the morbidity and mortality in elective cholecystectomy. The place of operative cholangiography in detecting stones in the common bile duct and in defining the anatomy of the individual case is well established;[5,10] other aids such as bile duct manometry and choledochoscopy have evolved with the same purpose, but are as yet of unproven efficacy.[7] The full value of operative cholangiography depends upon meticulous technique and accurate interpretation.

The value and the errors of one method of operative cholangiography was assessed in a prospective study with the aim of reducing further the incidence of unnecessary explorations and residual stones.

Materials and Methods

In a consecutive series of 207 patients undergoing cholecystectomy, operative cholangiography was attempted in 176 cases (85%). The clinical and other features of this series of patients have been described elsewhere.[2] In the remaining 31 patients, operative cholangiography was omitted for several reasons (Table 1). One-hundred forty two (69%) of cases had cholecystectomy alone, 65 patients (31%) had duct exploration as well.

The technique used to obtain operative cholangiograms was that described by Fraser and McNair,[4] using the cystic duct cannula of Aldrete and Judd,[1] in 172 cases and by needle puncture of the duct in 5 cases. Two films were usually obtained, using 5 ml and 9 ml Conray 280 60% respectively with the patient tilted 10° head down. A third film was retained in the cassette tunnel for the purpose of obtaining a post-exploratory t-tube cholangiogram should it be necessary. If the bile duct was explored, peroperative postexploratory t-tube cholangiography was usually attempted, and subsequently postoperative t-tube cholangiograms were performed in every case. Each patient was followed up carefully using intravenous cholangiography to demonstrate the ducts, where necessary. All cholangiograms were reviewed by two observers, the films being interpreted using the criteria suggested by Le Quesne.[8] In all cases except 6, i.e. 201 out of 207 (97%), adequate visualization of the biliary duct system was obtained by operative cholangiography, t-tube cholangiography or intravenous cholangiography at late followup. The 6 exceptions, not having had operative cholangiography, declined to have intravenous cholangiography on review, since they were asymptomatic.

Results

The gross results of treatment in this series were good, i.e. there were no deaths and few complications. Of the 174

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TABLE 1. *Operative Cholangiogram Omitted (31)*

Palpable common bile duct stones	17	17 (explored)
Radiographic equipment failed	2	14 (not explored)
Non availability of X-Ray equipment	3	
Electively omitted on clinical grounds	9	

TABLE 2. *Abnormal Operative Cholangiograms Not Explored (9)*

No visualisation of common hepatic duct	4 (one had residual calculus)
Overlying gas shadows or air bubbles obscured X-ray	3
Stricture lower end of common bile duct	1
No contrast into duodenum	1

TABLE 3. *Abnormal Operative Cholangiograms Explored Without Success (8)*

Surgeon recorded stone pushed into duodenum	4
Dilated duct—negative findings	2
No medium into duodenum prior to exploration	1
Artefact due to crossing of right hepatic artery	1

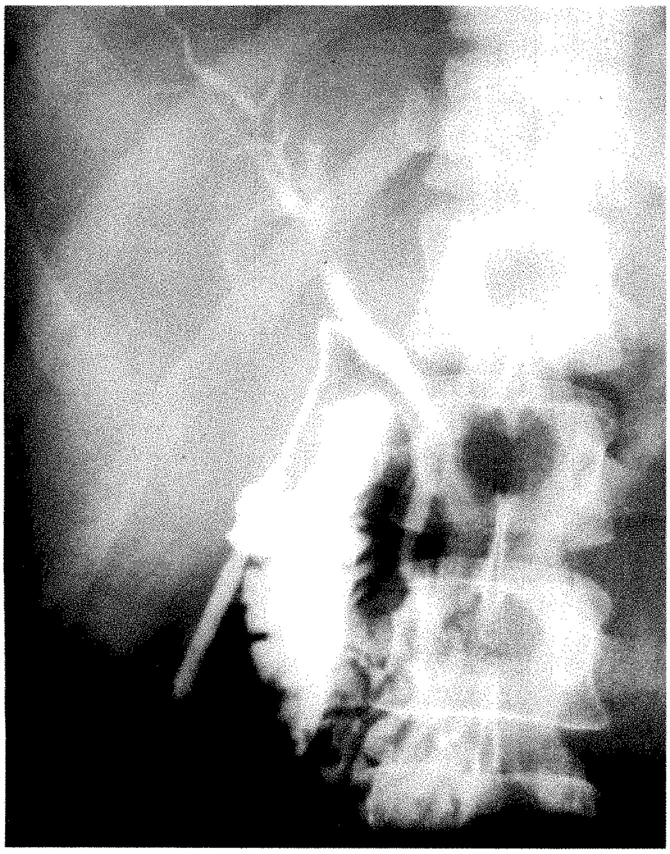


FIG. 1. Artifact due to right hepatic artery crossing common hepatic duct.

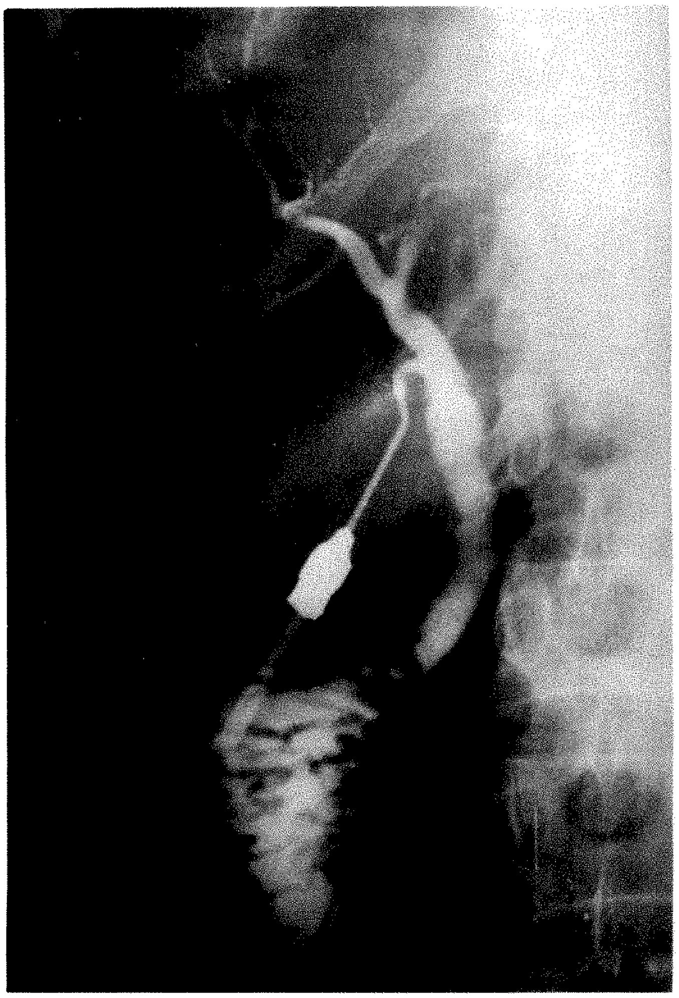


FIG. 2. Stone at lower end common bile duct which was not recovered but pushed through into duodenum.

successful operative cholangiograms, 129 were judged to be normal at the time of operation. In 2 of these, stones in the common bile duct were subsequently found: in one case the surgeon, at operation, palpated a stone despite an apparently normal X-ray and in the other patient, jaundice occurred 9 months after operation, a stone was identified on intravenous cholangiography and removed at a second operation. The false negative rate, therefore, was 1%.

Of the 45 operative cholangiograms judged abnormal at the time of operation, stones were recovered at operation in 35, and exploration was negative in 10. In the latter 10 patients, no stones were shown on postoperative t-tube cholangiography or on followup. There were, therefore, 10 false positives in 174 cholangiograms, 6%. Of the 35 patients who underwent exploration and in whom stones were recovered, 3 were found to have residual calculi on the postoperative t-tube cholangiogram and 2 subsequently required re-exploration. In only 1 of these was a stone recovered.

The above results show the accuracy of operative cholangiography as judged by the success of exploration of the ducts when indicated by the surgeon's interpretation of the operative X-rays at the time of operation. Using strict criteria[8] in the interpretation of the operative cholangiograms, 9 further cholangiograms might be considered abnormal and these had not been explored but in only 1 has a residual calculus been demonstrated. The radiological abnormalities in this group are shown in Table 2. In two of the patients undergoing exploration, the operative cholangiograms were subsequently judged to be normal and in fact exploration had been negative. In 8 patients the cholangiogram was still considered to be abnormal on review but exploration had been negative; the reasons associated with these apparent errors are listed in Table 3 and illustrated in Figs. 1–3.

Anomalies

Anomalies in duct architecture were noted in 21 (12%) of the 174 operative cholangiograms carried out (Table 4). The commonest anomaly encountered was drainage of the common bile duct into the third part of the duodenum in 10 (6%) cases (Fig. 4). Others encountered include an accessory right hepatic duct in 3 cases, and the cystic duct draining into the right hepatic duct in 2 cases (Fig. 5). These anomalies are of importance in avoiding injury to the duct system. There was a diverticulum of the lower end of the common bile duct in two cases. Both of these were associated with residual stones (Fig. 6) one requiring subsequent exploration and in the other the stones passing spontaneously after the t-tube had been clamped for 4 weeks.

TABLE 4. *Twenty-one Anomalies (12%)*

Bifid cystic duct	1
Long cystic duct	1
Cystic duct → RHD	2
Accessory RHD	3
CBD → 1st part of duodenum	1
CBD → 3rd part of duodenum	10 (6%)
CBD lower end anomaly	1
CBD diverticulum	1
Ampullary diverticulum	1

Complications

In 3 patients complications arose out of the use of operative cholangiography. In 1, leakage of the bile from a wound persisted for 7 days and may have been the result of needle cholangiography, and in another the cystic duct was torn on cannulation and subsequent exploration of the duct and t-tube drainage had to be carried out. In a third, the common bile duct was pierced by an over-sharpened cannula, and again exploration and t-tube drainage was embarked on to avoid biliary leakage following operation. In

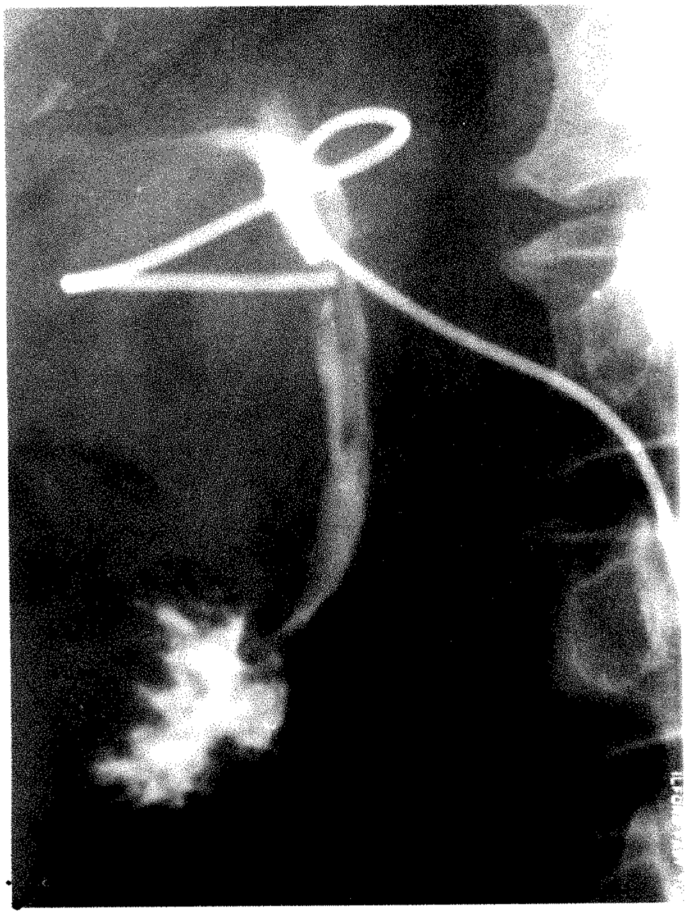


FIG. 3. Same patient as FIG. 2—postoperative T-tube cholangiogram.

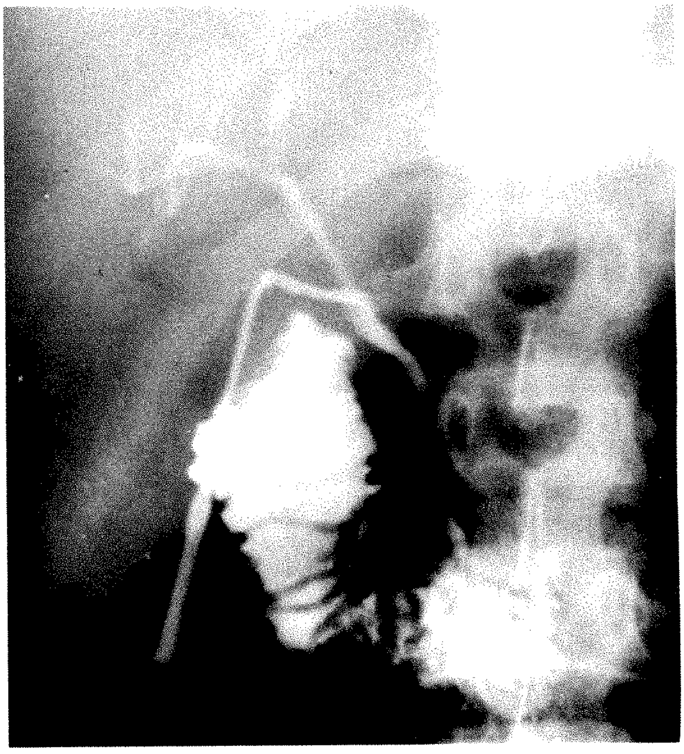


FIG. 4. Common bile duct draining into 3rd part of duodenum.

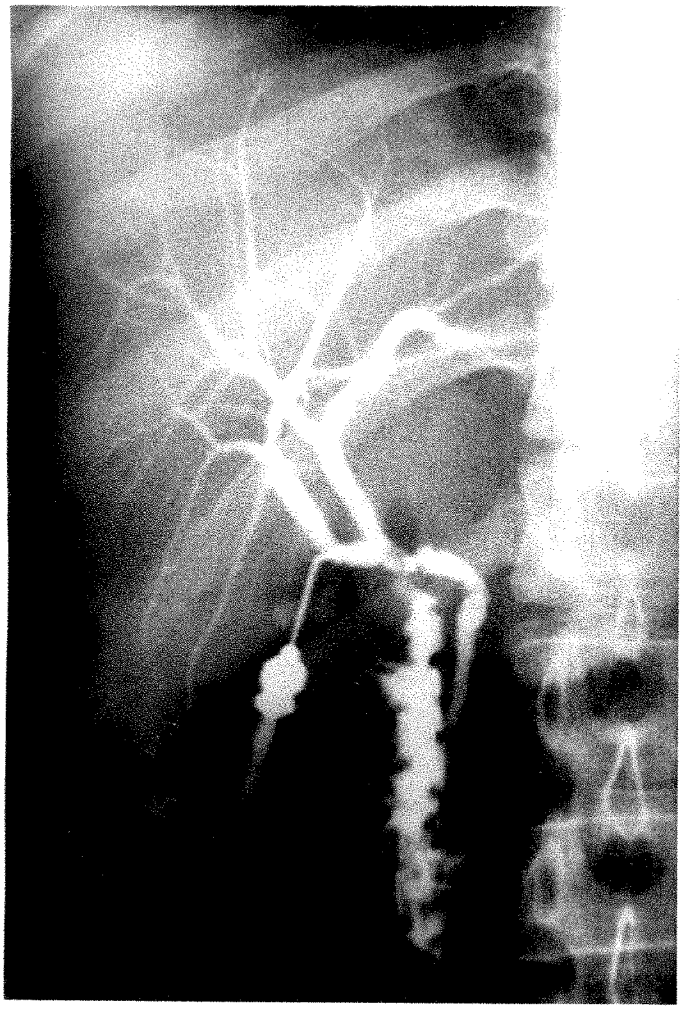
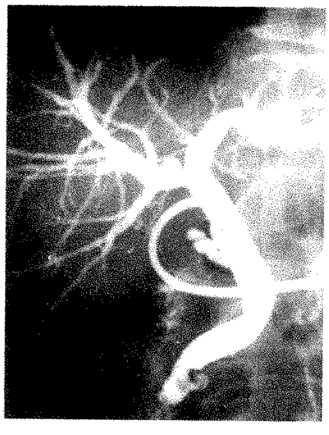


FIG. 5. Cystic duct draining into right hepatic duct.

none of these 3 cases was the complication serious and their convalescence was uncomplicated. There was one case encountered in this series of the syndrome first described by Walters and Bollman[11] and known in Edinburgh as the "Waltman Walters" Syndrome. This was not related to the use of operative cholangiography but was due to removal of the t-tube on the tenth day postoperatively and there was a subsequent collection of bile which required reoperation.

FIG. 6. Calculi in common bile duct diverticulum.



Other Features

In 34 (20%) of operative cholangiograms, contrast medium entered the pancreatic duct (Fig. 7). This was not associated with any symptoms of back pain, evidence of duct stones or postoperative pancreatitis. Entry of radioopaque dye into the pancreatic duct was also seen in 24% of the postoperative t-tube cholangiograms but was rare in the postexploratory peroperative cholangiogram.

Discussion

Of 176 cholangiograms, 172 were attempted using the cystic duct cannula and this was successful in 169 cases. Three failures by this technique consisted of one failure to cannulate a very narrow cystic duct and the other two cases referred to above (torn cystic duct, cannula piercing wall). Thus the technique was successful in 98% of cases.

Technical failure, false positive and false negative rates compare favourably with those of bile manometry and choledochoscopy as alternative methods of detecting stones in the common bile duct.[3,9] Our own experience with

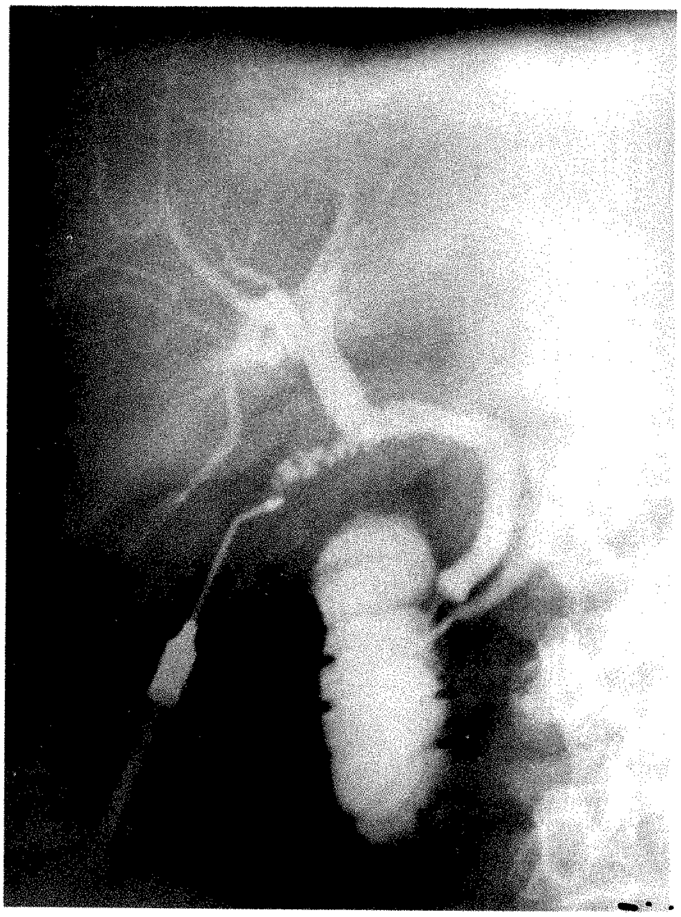


FIG. 7. Reflux of contrast medium into pancreatic duct—operative cholangiogram.

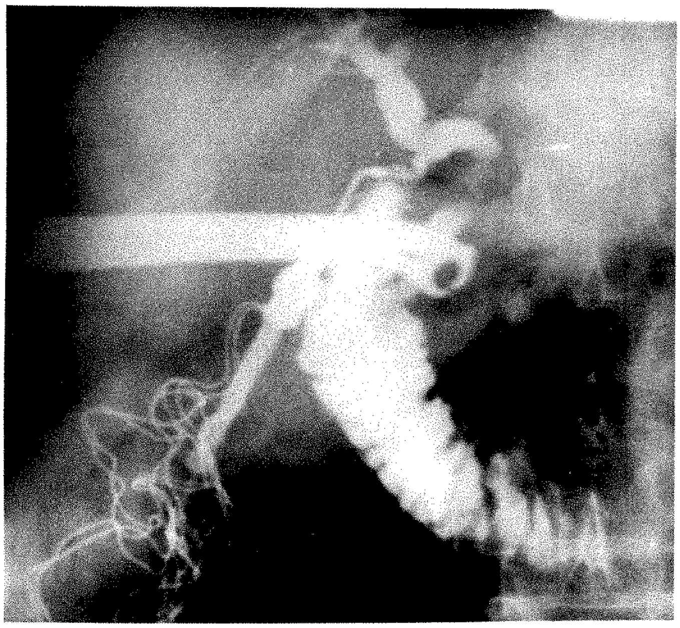


FIG. 8. Towel clip obscures the common bile duct.

choledochoscopy early in the series gave poor results. It was attempted in 15 cases, reasonable visualisation of the common bile duct and right and left hepatic ducts occurred in only 6, and in 2 of these, residual stones were found after operation despite apparent clearance. In reviewing the factors associated with negative exploration, failures of interpretation and technique are both present. The commonest cause is a stone being pushed into the duodenum, and the surgeon is generally aware of this. Failure to remove packs and instruments may obscure the lower end of the common bile duct (Fig. 8) or may prevent dye entering the duodenum. If the surgeon is unaware of possible artefacts caused by crossing of the right hepatic artery, exploration may be carried out unnecessarily. In the interpretation of the cholangiogram, failure to visualise the common hepatic duct occurred in 4 cases. None of these was explored but at late followup intravenous cholangiography, 1 has been shown to have a residual stone. For this reason it is important to visualise the hepatic ducts if necessary by tilting the table or occluding the lower end of the duct while dye is being injected for a third X-ray film. We would not, therefore, agree with Lawson and Gunn[6] and others that failure to demonstrate the hepatic ducts adequately is of little significance.

In 12% of our cases duct anomalies were demonstrated and the realization of this allowed for better and safer exploration of the ducts when required.

It is concluded from this prospective study that the criteria of Le Quesne[8] ought to be followed if the best results of operative cholangiography are to be obtained. The method used in this series proved simple, reliable and safe.

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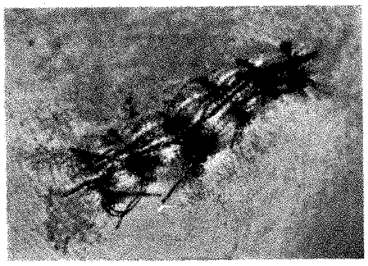

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